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Original Communications

I. THE FORM OF THE QRS COMPLEX IN THE NORMAL PRECORDIAL ELECTROCARDIOGRAM AND IN VENTRICULAR HYPERTROPHY

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THE origin and form of the QRS complex in multiple precordial leads has been elucidated, in particular by the work of Wilson and associates.[1-12] The presentation of these concepts to beginners is difficult, but has been facilitated in the courses at Wayne University during the past four years by the use of a series of diagrams, which reconstruct the portion of the QRS complex registered in each lead at fixed intervals after the onset of the initial deflection. Since a similar method of analysis has not been found in any of the published works on electrocardiography, it is presented to bring wider application as a teaching aid.

The Mode of Spread of the Activating Impulse Through the Ventricles.—The mode of spread of the activating impulse through the ventricles constitutes the basis for differences in multiple precordial leads and hence will be briefly reviewed as an introduction to the diagrammatic analysis. The impulse normally arises in the auricle, reaches the ventricles through the right and left branches of the bundle of His, and then fans out over the Purkinje network in the ventricular endocardium at an approximate rate of 40 millimeters per 0.01 second, arriving successively in the septum, anterior, lateral, and posterior walls.[13] As a result of this mode of spread, the impulse normally reaches the endocardial surface of the lateral wall approximately 0.02 second after its arrival in the septum. Upon reaching the endocardium, the impulse spreads centrifugally towards the epicardium at the comparatively slow rate of 4 millimeters per 0.01 second.[13] It reaches the epicardial surface of the anterior wall of the left ventricle after its arrival in the corresponding surface of the right ventricle, owing to the greater thickness of the intervening myocardium, and reaches the lateral and posterior surfaces of the left ventricle still later, because of its later start in these regions.

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During its passage from endocardium to epicardium, the impulse successively activates each responsive muscle cell in its pathway. The moment a cell is excited, it becomes negative in respect to the resting cells ahead of the advancing impulse. The negative potential of the excited cell is transmitted instantaneously to the endocardium and cavity; the positive potential of the as yet unactivated cells is transmitted similarly to the epicardium and overlying skin surface.

The potential of a precordial electrode roughly parallels that of the epicardial surface which it subtends. The potential of a given area of epicardium is governed largely by the state of the underlying segment of myocardium, but is influenced by activation of the remainder of the ventricular wall to a degree inversely proportional to the cube of the intervening distance.[4] As long as an impulse is advancing through, and activating, the subjacent myocardium, it causes increasing positivity of the overlying epicardium and precordium, resulting in the registration of an upstroke or R wave through an exploring electrode applied to either surface. Upon arrival at the epicardium and extinction of the impulse, surface positivity suddenly disappears, resulting in the registration of a precipitous downstroke.* In direct epicardial leads, this downstroke or intrinsic deflection is nearly perpendicular; in precordial leads, it is less precipitous, owing to the larger surface from which it is derived, and is consequently designated as the intrinsicoid deflection. When activation of the opposite wall begins in advance of the arrival of the impulse in the segment beneath the exploring electrode, negative potentials referred to the cavity are transmitted through the as yet unactivated segment to the overlying epicardium and precordium, and are recorded as an initial downstroke or Q wave. When activation of the opposite wall continues after extinction of the impulse in the epicardium beneath the exploring electrode, negative potentials referred to the cavity are transmitted through the depolarized segment to overlying epicardium and precordium, resulting in the continuation of the intrinsicoid deflection below the isoelectric line as an S wave.

As a result of the asynchrony in onset and completion of activation of different portions of the ventricles, the QRS complex recorded through any precordial lead facing the ventricular surface should consist of at least two phases, i.e., either a QR or RS deflection. Furthermore, a series of precordial leads taken so as to cover the surface of the right and left ventricles must show significant differences in QRS patterns. The form and interrelations of the component phases of the QRS complexes in the six Wilson precordial leads will be brought out by means of diagrams analyzing the normal electrocardiogram and the electrocardiogram in left ventricular hypertrophy and right ventricular hypertrophy.

Analysis of the Normal Precordial Electrocardiogram.—The first subject was a young adult, whose heart was normal to clinical and roentgenological examination. The QRS deflection was 0.08 second in duration and was normal in contour in all leads. The precordial electrocardiogram is reproduced in Fig. 1 and

*Although it has been contended that excitation of the subepicardial layer of muscle is not completely extinguished until some time during the course of the registration of downstroke of the R wave,[12] the peak of the R wave is taken as the index of the arrival of the impulse at the epicardial surface in these articles because it constitutes an accurate reference point for temporal measurements.

is analyzed through a set of four diagrams. In the first drawing (Fig. 1, *a*) that portion of the QRS which was registered in each lead during the first 0.01 second after the onset of the complex is accurately reconstructed and is accompanied by a schematic reproduction of the probable state of ventricular activation at the end of the first 0.01 second. The second, third, and fourth drawings carry on in a similar fashion, respectively reproducing the portion of the QRS completed by the end of 0.02, 0.04, and 0.06 seconds, together with the probable status of ventricular activation at the end of each period. Since the precordial leads in this and in subsequent figures were taken consecutively rather than simultaneously, this analysis is subject to error in the event that a portion at the beginning or end of the QRS complex happened to be isoelectric.

The grid on which the electrocardiographic drawings were made was two and one-half times the square millimeter markings of the electrocardiogram taken at the customary camera speed. This was done in order to separate the upstroke and downstroke of the QRS complex sufficiently so that each could be clearly identified in the drawing. The time interval, as measured on a horizontal plane between any two vertical lines, is 0.04 second, and that between each fifth black line is 0.20 second, thus corresponding with the electrocardiographic tracing. The amplitude of the tracing, as measured in millimeters in the drawing, is the same as in the original electrocardiogram, and thus the amplitude is not subjected to the magnification ($\times$ 2.5) employed for the time intervals.

In the cross sectional diagrams, the portion of the ventricle over which the electrode was presumably centered is indicated by a dot for each of the six leads. Since the electrode was placed on the precordium at some distance from the epicardium, it subtended a much larger ventricular area than is represented in the diagram. The sign adjacent to each dot was determined from the direction that the string was taking up to the moment depicted in the diagram. Thus the registration of an upstroke in a precordial lead indicates that the electrode was becoming increasingly positive and is represented by a plus sign at the corresponding epicardial dot; the registration of a downstroke signifies that the potential of the exploring electrode is changing in the opposite direction and is represented by a minus sign. The sign in the cavity denotes the potential of the endocardial surface at the same moment. The course of the impulse through the segment of wall subjacent to each of the six precordial positions is represented by arrows. The beginning of the upstroke in a given lead is taken as the reference point for the start of the impulse through the underlying subendocardial layer, whereas the peak of the upstroke marks the arrival of the impulse at the epicardial surface. The arrowhead represents the approximate position of the activating impulse at the moment depicted in the diagram, as judged by the portion of the ascending limb of the R wave completed at that moment. When the phase illustrated in the diagram antedates the arrival of the impulse or follows the completion of its passage through a given segment of myocardium, the arrow is omitted. Under these circumstances, potentials created by activation of other portions of the ventricle and referred to the cavity are transmitted through inert segments to the overlying exploring electrode, as indicated in the figures by parallelism in the potentials of the endocardial and epicardial surfaces.

Preliminary reference to the original electrocardiogram (Fig. 1) reveals that the QRS complexes at V_2 and V_3 resemble closely that recorded at V_1, whereas the QRS complexes at V_4 and V_5 are much like that at V_6. The striking contrast in the form of the QRS complex in V_3 and V_4 indicates that the electrode in its shift from one position to the next has crossed the interventricular septum. Thus, in this case, the electrode at positions V_2 and V_3, like that at V_1, is dominated by the potential variations of the epicardial surface of the right ventricle, whereas the electrode at positions V_4 and V_5, like that at V_6, is dominated by the potential variations of the epicardial surface of the left ventricle.[4]

The initial upstroke in right ventricular leads V_1 and V_2 indicates early positivity of the epicardial surface of the right ventricle. Since an early R wave has been demonstrated in leads from the right ventricular cavity of dogs and human subjects,[14] the endocardial surface of the right ventricle is also electropositive initially, as illustrated in Fig. 1, *a*. The R wave in leads from the right ventricular cavity and at least a portion of that in leads from the right precordium is derived from electromotive forces originating in the septum and is due to earlier onset of activation of the left side of the septum,[15] as illustrated in Fig. 1, *a*, and/or to greater magnitude of the forces developed through activation of the left than the right half of the septum, as indicated by the disproportion between the septal arrows in Fig. 1, *b*. Passage of the impulse through the free wall of the right ventricle, as represented in Fig. 1, *b*, also contributes to the R wave in leads from the right precordium. The attainment of the peak of the R wave in Leads V_1 and V_2 by the end of 0.02 second and the onset of the intrinsicoid deflection immediately thereafter indicate early extinction of the positive potentials referred to the right during septal activation and early arrival of the impulse at the epicardial surface of the right ventricle, as depicted in Fig. 1, *b*. The brief time required for the impulse to traverse the free wall of the right ventricle is attributable to the thinness of this structure in normal persons. The general resemblance of the tracing at position V_3 to that at V_1 and V_2 indicates that this lead is likewise dominated by the potential variations of the right side of the heart. The greater amplitude of the R wave at V_3 than at V_2 and V_1, together with the later attainment of the peak, is attributable to greater admixture of positive potentials derived from activation of the nearby anteroseptal wall of the left ventricle.

The initial upstroke in Lead V_4, taken from the vicinity of the antero-apical wall of the left ventricle, is a manifestation of the early arrival of the impulse at the left apex, as illustrated in Fig. 1, *a* and as demonstrated in the exposed human heart.[5] The continuing ascent of the R wave in V_4 after the period of 0.02 second signifies that the impulse is still in progress through the antero-apical wall of the left ventricle. The significantly longer time required for activation of the anterior wall of the left than the right ventricle is attributed to the normal difference in thickness.

The fact that the initial movement of the string is upward at V_4 and downward at V_5 and V_6 indicates that the impulse has reached and begun to activate the antero-apical portion of the left ventricle subjacent to position V_4 prior to its arrival in the anterolateral and lateral walls facing positions V_5 and V_6. The

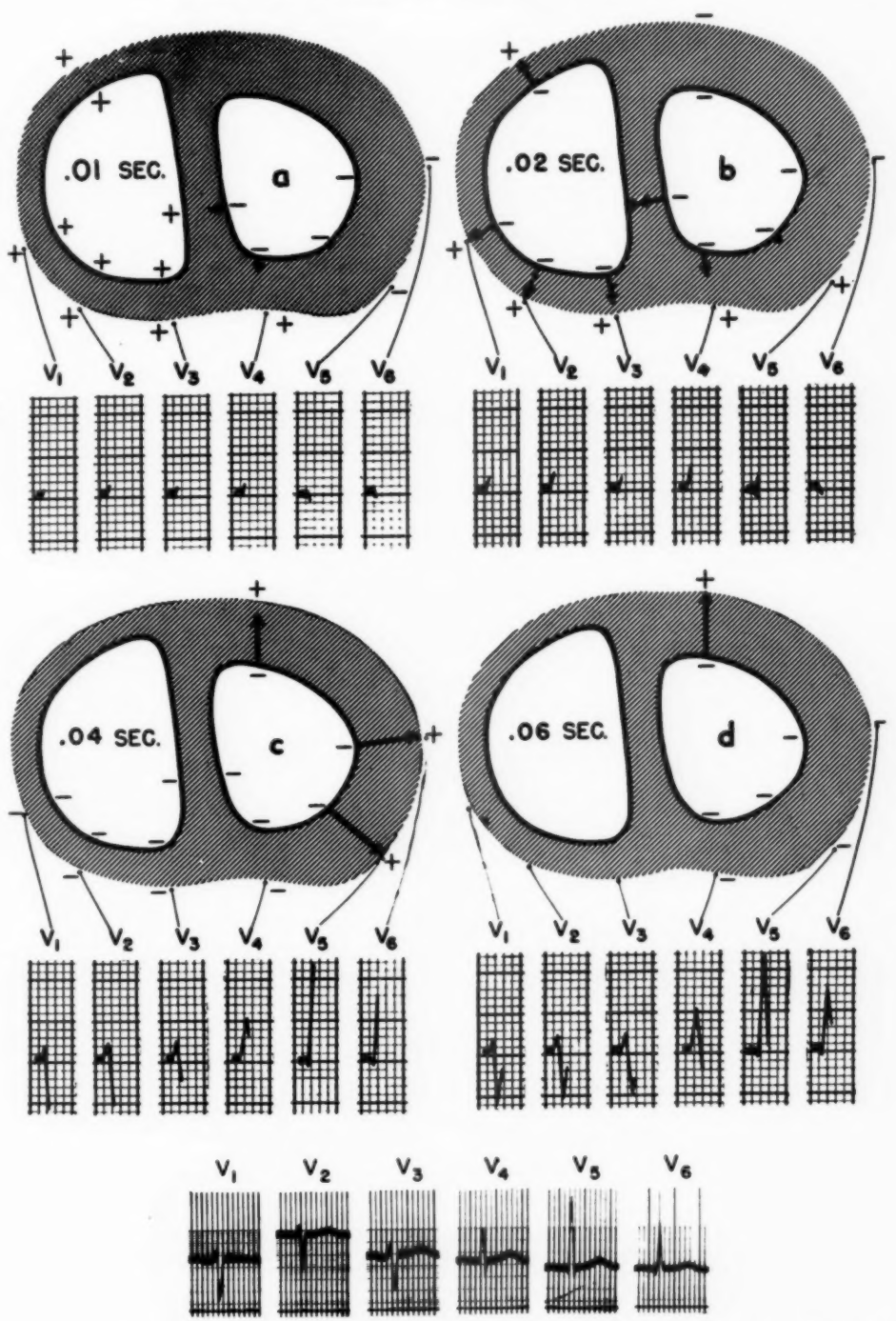

Fig. 1.—Normal precordial electrocardiogram. Diagrammatic reconstruction of the portion of the QRS complex registered in each lead and the probable status of ventricular activation at intervals of 0.01, 0.02, 0.04, and 0.06 second after the onset of the initial deflection.

antecedent onset of activation of the septum and antero-apical wall of the left ventricle causes increasing negativity of the ventricular cavity, which is transmitted through the as yet unactivated lateral wall, producing Q waves at V_5 and V_6, as illustrated in Fig. 1, *a*. The downward movement, or Q wave, at V_5 lasts for 0.01 second, when it is suddenly replaced by an upward movement, or R wave, marking the onset of activation of the subendocardial muscle of the anterolateral aspect of the left ventricle, as represented by the arrowhead in Fig. 1, *b*. Activation of the lateral wall beneath V_6 begins somewhat later, the downward movement of the string continuing for a total of 0.02 second. The fact that the Q waves in V_5 and V_6 last but 0.01 and 0.02 second, respectively, and are succeeded by R waves whose amplitude is at least four times as great indicates that these Q waves are within normal limits.[16,17] Both their duration and magnitude are explainable by the normal difference in onset of activation in the septal and lateral walls of the left ventricle.

An upward movement of the string begins in Lead V_6 immediately after the expiration of the 0.02 second interval, and marks the arrival of the impulse in the subendocardial layer of the lateral wall. The activation of the lateral wall of the left ventricle proceeds rapidly thereafter and the peak of the R wave, heralding the arrival of the impulse at the epicardial surface, is attained by the end of 0.04 second (Fig. 1, *c*). Meanwhile the peak of the R wave at V_4 has been passed and the intrinsicoid downstroke is in progress at the end of 0.04 second. During the interval between 0.02 and 0.03 second, the upstroke of the R wave in right ventricular leads V_1, V_2, and V_3 has given way to an intrinsicoid movement, which reaches the isoelectric line by the end of 0.03 second. This downstroke does not stop at the isoelectric line, but continues below as an S wave, due to the fact that the left ventricular cavity potentials, which are becoming increasingly negative as a result of activation of the lateral and posterior walls of the left ventricle, are now transmitted through the completely depolarized septum and right ventricular wall to positions V_1, V_2, and V_3. By the end of 0.06 second (Fig. 1, *d*), the entire outer wall of both ventricles has been activated, as shown by the fact that the string does not digress further from the isoelectric line in any lead. During the interval from 0.06 to 0.08 second, the potentials of both the cavity and epicardial surfaces rapidly return to zero.

The progressive increase in the amplitude of the R wave and in the length of the interval from the onset to the peak of the R wave as the electrode is moved from position V_1 to V_5 is a normal finding[16,17] and merely reflects the normally increasing thickness of myocardium beneath the exploring electrode.

The interval from onset to peak of the R wave in Leads V_1 and V_2 provides an index of the time elapsing between the onset of septal activation and the arrival of the impulse at the epicardial surface of the right ventricle, and the measurement of 0.02 second represents a typical normal finding. The interval from the onset of the QRS complex to the peak of the R wave in Leads V_5 and V_6 provides an index of the time elapsing between the onset of septal activation and the arrival of the impulse at the epicardial surface of the anterolateral wall of the left ventricle, and the measurement of 0.04 second is below the normal limit of 0.05 second. The interval from onset to the peak of the R wave in the same

leads furnishes an index of the time required for the impulse to pass from the endocardial to the epicardial surface of the anterolateral wall of the left ventricle, and the maximal measurement of 0.03 second is below the normal limit of 0.04 second.

The fact that the S wave is deepest at V_1 and V_2 and progressively diminishes as the electrode is moved further to the left is an aftermath of the normal differences in time of completion of activation. The S wave is deepest over portions of the ventricles where activation is completed earliest, because of the longer time interval available for the transmission of negative cavity potentials to the overlying precordial electrode. The absence of an S wave from Lead V_6 indicates that the lateral wall was one of the last portions of the ventricles to become depolarized, the cavity potential having returned to zero by the time the intrinsicoid deflection was completed in this lead.

Left Ventricular Hypertrophy.—In Fig. 2, the precordial electrocardiogram of a young woman with typical clinical and roentgenological signs of left ventricular hypertrophy due to hypertension is reproduced and analyzed in a manner similar to that carried out in Fig. 1. The QRS interval measures 0.11 second, and thus exceeds the customary range in normals, but falls short of that in bundle branch block. The transitional zone in Fig. 2, like that in Fig. 1, is between positions V_3 and V_4. The first three leads reflect principally the potential variations of the right side of the septum and epicardial surface of the right ventricle; the last three, those of the left side of the septum and epicardial surface of the left ventricle.

The first drawing (Fig. 2, *a*) represents a reconstruction of that portion of the QRS complex registered in each lead during the first 0.02 second, accompanied by a cross section of the ventricle, showing the presumptive state of ventricular activation at the end of the period. A study of this drawing reveals that the initial deflection in Leads V_1, V_2, and V_3 is upright and reaches its peak within the first 0.02 second, signifying early onset and completion of right ventricular activation, similar in every respect to that found in normal tracings reproduced in Fig. 1. The initial upstroke in Lead V_4, facing the anteroseptal wall of the left ventricle, signifies early arrival of the impulse in that region in left ventricular hypertrophy, as in the normal. An initial R wave is also recorded in Lead V_5. The fact that the portion of the R wave recorded in the first 0.02 second is slightly smaller at position V_5 than at V_4 is presumably referable to a slightly later arrival of the impulse in the subendocardial muscle beneath position V_5. The delay in arrival of the impulse in the portion of the lateral wall subtended by the electrode at position V_6 is sufficient to permit the registration of an initial downstroke, reflecting cavity potentials transmitted through the as yet unactivated lateral wall. Since the downstroke of the Q wave in Lead V_6 is only 0.02 second in duration and is much less than 25 per cent of the amplitude of the succeeding R wave, this Q wave is entirely normal and quite comparable to that in the corresponding lead of Fig. 1.

The striking feature of the next two drawings, representing the state of activation at the end of 0.04 and 0.06 second, respectively, is the increased duration and amplitude of the R wave in left ventricular leads in comparison

with the normal findings, as reproduced in drawings at similar time intervals in Fig. 1. The string is still moving upward at the end of 0.04 second in the records taken at positions V_4, V_5, and V_6, indicating that the impulse is still in progress through the left ventricular wall, as shown by the arrowhead in the second drawing. The attainment of the peak of the R wave, marking the arrival of the impulse at the epicardial surface, requires a total of 0.05, 0.06, and 0.07 second from the beginning of the QRS complex in Leads V_4, V_5, and V_6, respectively, of which 0.05 second is consumed in recording the upstroke of the R wave. The increased time interval from the onset of the Q wave to the peak of the R (and from onset to peak of R), coupled with the increased amplitude of the R wave in leads over the left ventricle, differentiate the QRS complex of this case from the normal illustrated in Fig. 1 and are diagnostic of left ventricular hypertrophy.[4,12,18] The increased thickness of myocardium, which must be traversed, accounts for the longer time consumed and the greater voltage developed.

The lengthened interval required for left ventricular activation makes a longer time available for the transmission of the negative potentials of the left ventricular cavity through the septum and the right ventricular wall. Thus, the intrinsicoid movement in right ventricular leads V_1, V_2, and V_3 continues downward as an exceptionally deep S wave, which, like the tall R wave in left ventricular leads, is a feature of left ventricular hypertrophy. A small, but definite, S wave is registered in V_4, due to continuing activation of other portions of the left ventricle after completion of depolarization of the anteroseptal wall. The absence of an S wave from Leads V_5 and V_6 is in keeping with late completion of activation of the lateral wall of the left ventricle.

The slurring or notching of the ascending limb of the R wave in Lead V_4 and of the descending limb of the S wave in V_3 are common findings in leads near the transitional zone and probably reflect the arrival of the impulse at the epicardial surface of the anterior terminus of the septum or the opposite ventricle. The slurring of the downstroke of the S wave in V_3 is synchronous with the peak of the R wave in V_4 and apparently reflects the arrival of the impulse at the epicardial surface of the anteroseptal wall of the left ventricle. The slurring of the upstroke of the R wave in V_4 occurs later than the peak of the R wave in right ventricular leads V_1, V_2, and V_3, but earlier than the peak of the R wave in left ventricular leads, and may be due to arrival of the impulse at the epicardium covering the anterior terminus of the intervening septum.

The depression of the RS-T junctions and deep inversion of the T waves in left ventricular leads V_4, V_5, and V_6 and the reciprocal RS-T and T patterns in right ventricular leads V_1 and V_2 are characteristic findings in uncomplicated left ventricular hypertrophy, but are beyond the scope of this discussion.

Right Ventricular Hypertrophy.—In Fig. 3, the precordial electrocardiogram of a young woman with typical clinical and roentgenological signs of right ventricular hypertrophy due to mitral stenosis is reproduced and analyzed in a manner similar to that employed in Figs. 1 and 2. The duration of the QRS complex is 0.10 second. A quick perusal of the tracings shows a striking difference from the normal and an approximate reversal of the pattern of left ventricular hypertrophy depicted in Fig. 2. The tracings recorded at positions V_1 and V_2

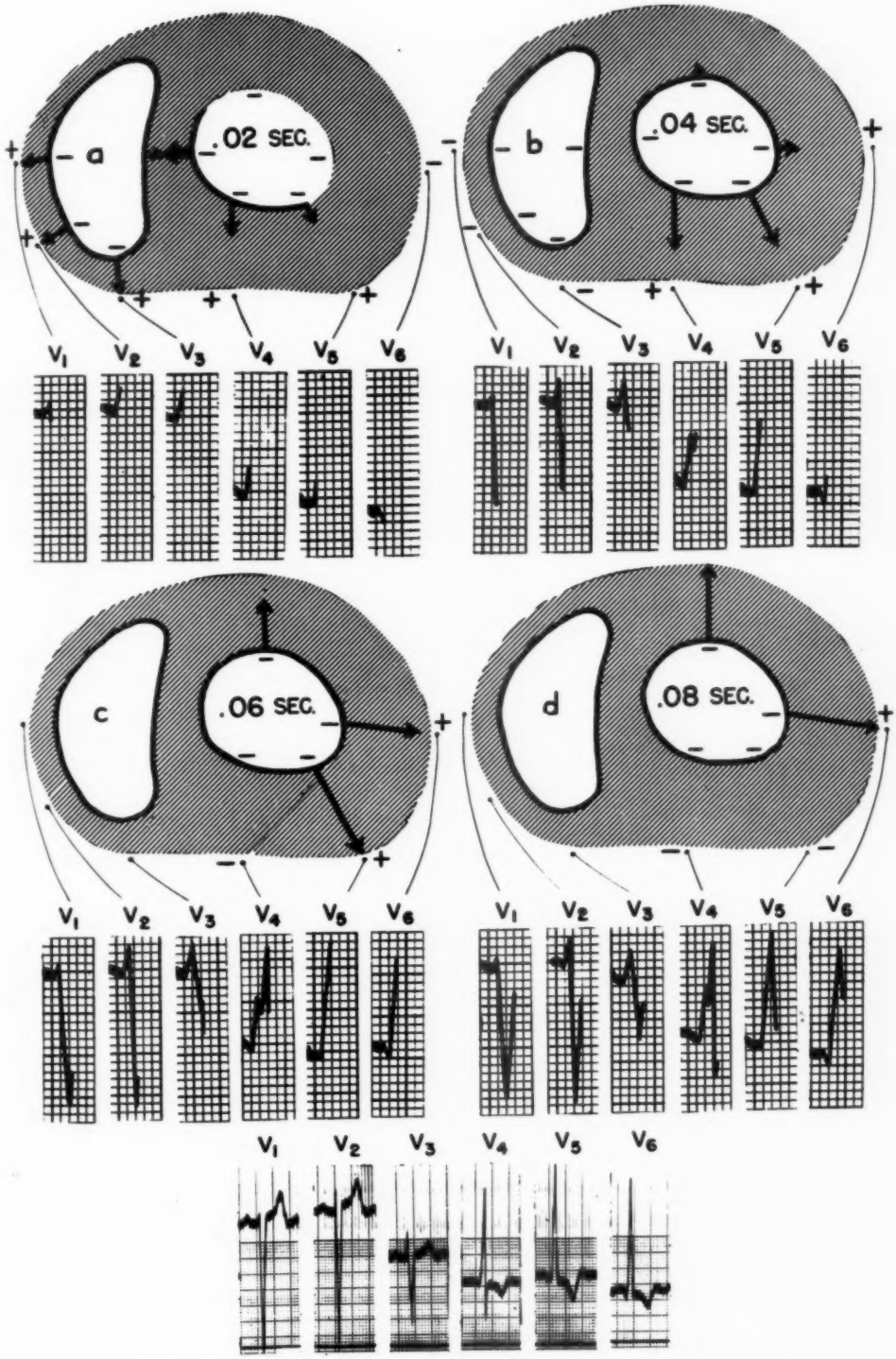

Fig. 2.—Precordial electrocardiogram in left ventricular hypertrophy. Diagrammatic reconstruction of the portion of the QRS complex registered in each lead and the probable status of ventricular activation at intervals of 0.02, 0.04, 0.06, and 0.08 second after the onset of the initial deflection.

in this case resemble those obtained at positions V_6 and V_5 in left ventricular hypertrophy, whereas the pattern in Leads V_6 and V_5 of this case is more representative of that customarily found in Leads V_1 and V_2. The general resemblance of the QRS complex in Lead V_3 of Fig. 3 to that of V_2 and V_1 suggests that the precordial electrode at the V_3 position is dominated by right ventricular potentials, and the general resemblance of the QRS of V_4 to that of V_5 and V_6 suggests that the precordial electrode in this location is dominated by left ventricular potentials. Further details are brought out through a study of the portions of the QRS completed in each lead at the end of 0.02, 0.04, and 0.06 second, respectively.

The initial deflection is upright in Leads V_6 and V_5 as well as in V_4 of this case, indicating early activation of the lateral as well as the anterior aspect of the left ventricle. Furthermore, the peak of the R wave is attained in leads over the left ventricle in the very short span of 0.02 second, suggesting early arrival of the impulse at the epicardial surface of the anterior and lateral walls of the left ventricle. The early completion of left ventricular activation, taken in conjunction with the physical signs of marked mitral stenosis, would raise the question of left ventricular atrophy secondary to impairment of left ventricular filling.

The initial deflection in Leads V_2 and V_3 is upright, but the QRS complex in V_1 apparently begins with a minute Q wave, which is quickly replaced by an upstroke. More distinct Q waves have been recorded in Lead V_1 in other cases subsequently proven to have uncomplicated right ventricular hypertrophy at autopsy.[19] In a recently reported case of tetralogy of Fallot with a comparable qR complex in Lead V_1,[20] a simultaneous lead from the right ventricular cavity also showed an initial downstroke, synchronous with that in V_1. This observation demonstrated that the Q wave in Lead V_1 reflected an initial negativity of the right ventricular cavity, possibly due to septal activation from right to left. If the right ventricular cavity were likewise initially negative in the present case, the registration of an initial upstroke in Leads V_3 and V_2 facing the anteroseptal wall of the right ventricle would indicate early onset of activation of the underlying subendocardial layer, whereas the Q wave in Lead V_1 facing the anterolateral wall of the right ventricle would indicate sufficient delay in arrival of the impulse to permit momentary transmission of cavity potentials to the surface.

The most striking features of Leads V_1, V_2, and V_3 are the unusually tall R wave, the late onset of the intrinsicoid deflection, and the small or absent S wave. From a study of the portion of the tracing completed in the first 0.02 second (Fig. 3, *a*), it would appear that the impulse has reached the epicardial surface of the lateral wall of the left ventricle, as shown by the attainment of the peak of the R wave in Leads V_5 and V_6, but has only activated a fraction of the right ventricular wall, as shown by the relatively small portion of the R wave registered in Leads V_1, V_2, and V_3. The continuing upstroke in right ventricular leads during the next 0.02 second (Fig. 3, *b*) and the requirement of a total of 0.04 to 0.05 second for attainment of the peak of the R wave in these leads are typical of right ventricular hypertrophy.[4,12,19] The registration of the descending limb of the S wave in Leads V_5 and V_6 synchronously with the upper portion of the

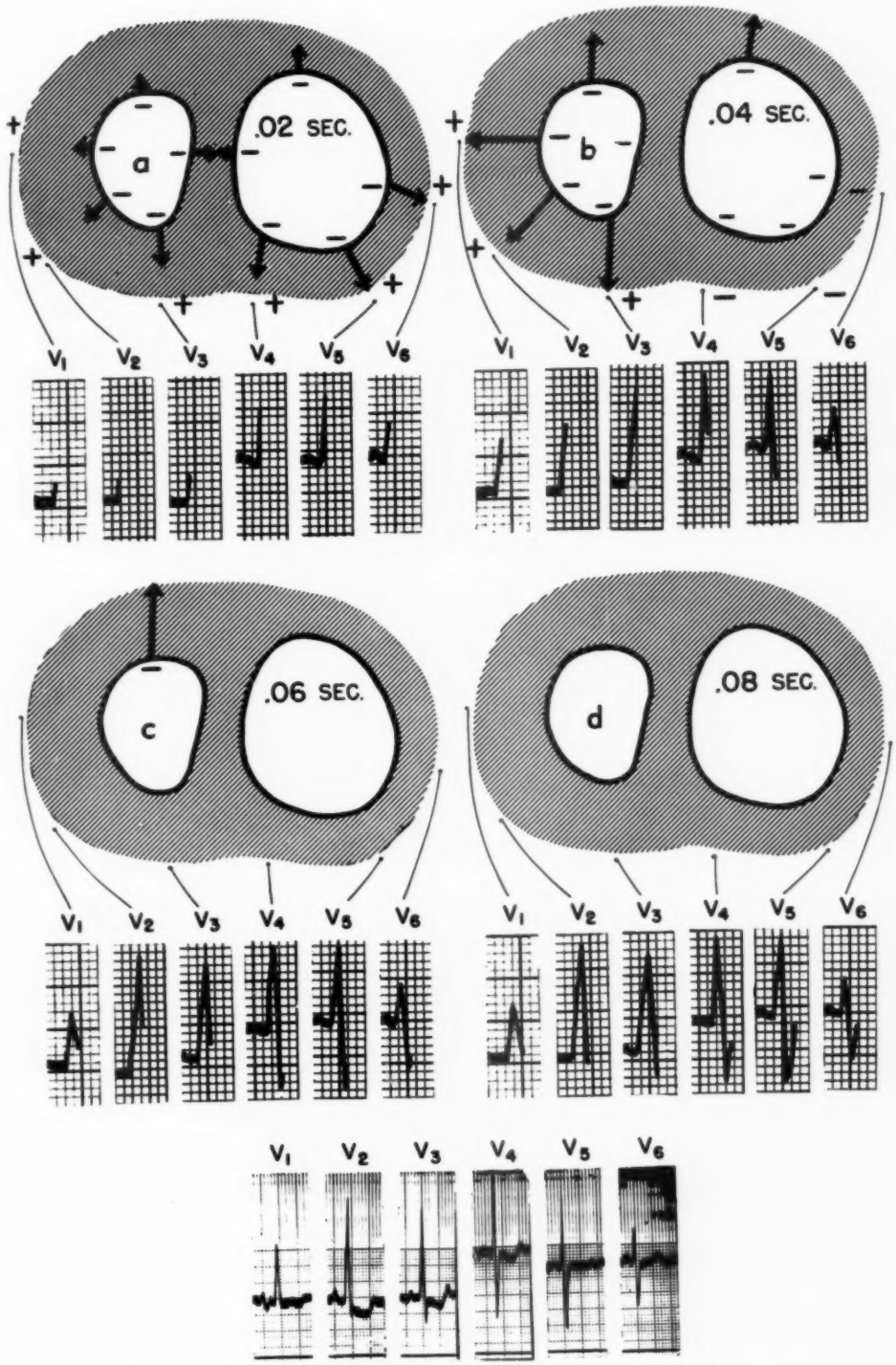

Fig. 3.—Precordial electrocardiogram in right ventricular hypertrophy. Diagrammatic reconstruction of the portion of the QRS complex registered in each lead and the probable status of ventricular activation at intervals of 0.02, 0.04, 0.06, and 0.08 second after the onset of the initial deflection.

ascending limb of the R wave in V_1 and V_2 points to a common origin and suggests that the S wave is due to transmission of negative right ventricular cavity potentials through the depolarized septum and anterolateral walls of the left ventricle to the left axilla. The presence of a small S wave in Lead V_3 facing the anteroseptal wall of the right ventricle, together with its absence from V_1, would indicate completion of activation of the anteroseptal wall of the right ventricle sufficiently ahead of the lateral wall to permit brief transmission of negative cavity potentials to the surafce.

Although the contour of the RS-T segment in Leads V_2 and V_3 suggests digitalis action, the patient had received no cardiac glycosides. The depressed RS-T junctions and inverted to diphasic T waves in Leads V_1, V_2, and V_3 are also referable to right ventricular hypertrophy.

SUMMARY

The form and interrelations of the component phases of the QRS complexes in the six Wilson precordial leads are demonstrated through a diagrammatic reconstruction of the portion of the QRS registered in each lead at fixed intervals after the onset of the initial deflection. This method of analysis is offered as a teaching aid and is employed to bring out the characteristic features of the QRS complex in the normal precordial electrocardiogram, in left ventricular hypertrophy, and in right ventricular hypertrophy.

The illustrations were made by Miss Evelyn Erickson, assisted by Miss Geraldine Chesney.

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THREE UNUSUAL CASES OF PARASYSTOLE

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TRUE parasystole with simple interference of two rhythms is not exceedingly rare. It can be found in our experience, in about 0.04 per cent of routine electrocardiograms obtained in a general hospital. In these patients an automatic ectopic center, usually situated in the ventricles, forms rhythmic stimuli without being disturbed by the prevailing rhythm. These stimuli elicit a ventricular contraction whenever they arise outside of the refractory phase of the ventricles. Because of interference between sinus and automatic rhythms, some automatic stimuli are formed just when a sinus stimulus spreads over the ventricles. In this instance one part of the ventricles will be activated by the sinus stimulus and another by the automatic stimulus. In this way "combination" (summation, fusion) beats appear in the electrocardiogram.

An additional consequence of the interference of two rhythms and therefore a cardinal sign of parasystole is the continuous variation of the length of the coupling, that is, of the distance between automatic, ectopic beats and the preceding beat of the basic rhythm.

Parasystole would be overlooked less often if its presence was suspected and long tracings examined whenever heterotopic beats appear without fixed coupling to the preceding normal beat. In simple extrasystole with which parasystole is often confused, the coupling is usually constant (fixed).

In this report three cases of parasystole will be described which show unusual, and, to our knowledge hitherto unpublished patterns.

CASE REPORTS

CASE 1.—The 70-year-old man was admitted because of a traumatic fracture of the lateral condyle of the right femur. The presence of pernicious anemia had been discovered three years earlier; the admission erythrocyte count was 3.2 millions and the hemoglobin was 11.5 grams. The heart was of normal size and shape and a rough systolic murmur was audible over the apex. The blood pressure was 120/80 mm. of mercury. Fluoroscopy was uninformative save to substantiate the presence of pulmonary emphysema. Many premature beats were noted on auscultation and were attributed to extrasystoles.

Electrocardiograms: The first electrocardiogram, obtained on admission (Fig. 1) shows a sinus rhythm with a rate of 78 and a P-R interval of 40.* The ventricular complexes are normal in the standard leads and in CF_5. Frequently ventricular beats appear after a shorter P-R interval. Thus, the third ventricular complex in Lead I, the third and fifth in Lead II, the fourth and the sixth in CF_5 follow the preceding P wave at an appreciably shorter distance than the others.

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*The duration of P-R intervals or P-P and R-R distances are given in hundredths of a second. Therefore 40 means 0.40 second.

Since the short P-R interval apparently prevails when the corresponding P wave appears early in diastole shortly after the preceding T wave, a supernormal phase of conductivity was suspected. In tracings exhibiting the latter phenomenon auricular contractions which appear soon after the preceding beat may be conducted to the ventricle faster than those which appear later in diastole.[9]

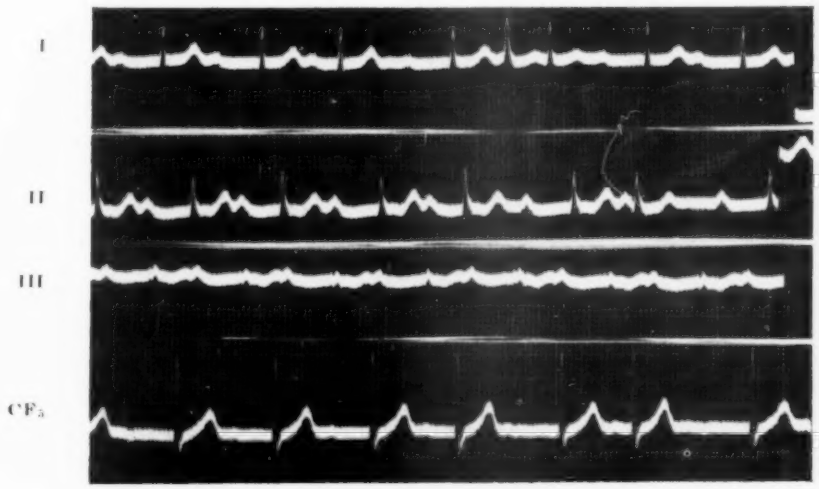

Fig. 1.—Three standard leads and CF_5 of Case 1 showing parasystole with ectopic focus in the A-V conduction system above its bifurcation.

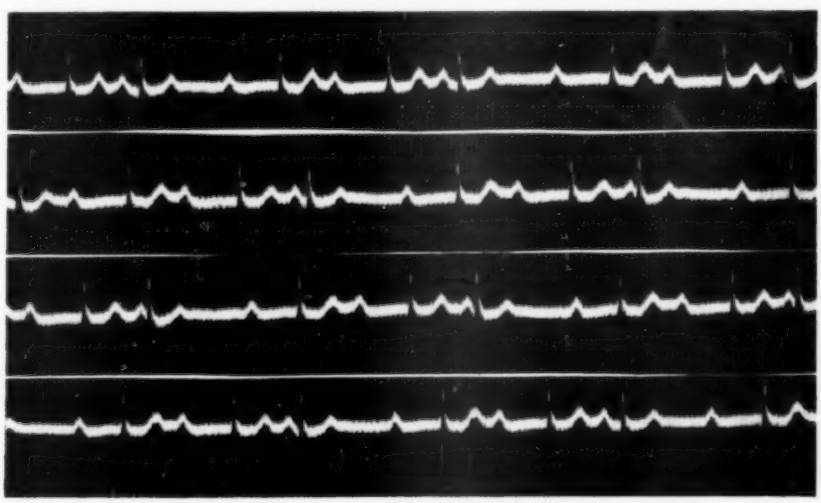

Fig. 2.—The four tracings are continuous (Lead II) and show paraystole with simple interference of two rhythms.

If, however, a supernormal phase of conduction were present, the fifth and the sixth systole in Lead I as well as the seventh in Lead II could hardly be explained in the same manner; therefore another interpretation was sought.

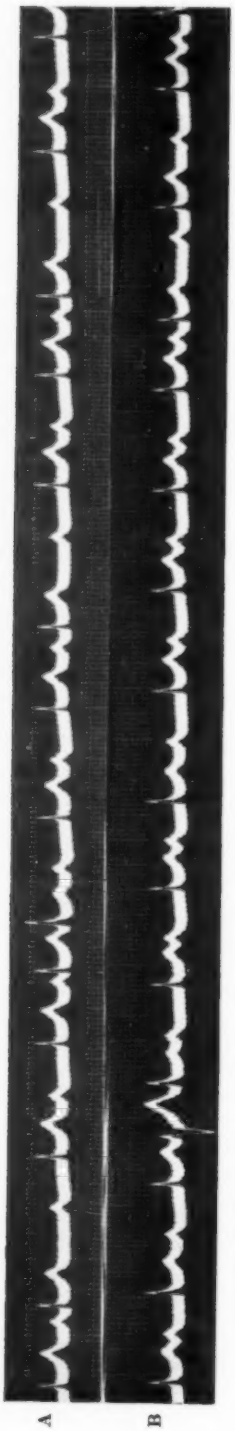

Fig. 3.—Two tracings showing unusual patterns of parasystole and prolongation of the ectopic period following interpolation of an ectopic, parasystolic beat.

If the interval between the fourth and the sixth ventricular complex in Lead CF^5 is measured one finds it to be 138 (1.38 second) long. The distances between the third and fifth abnormal ventricular complexes in Lead I, or between the third, fifth, and seventh abnormal beats in Lead II measure 135. This close similarity of the intervals suggests the presence of an independent focus which forms rhythmic stimuli. This suspicion is confirmed by examination of longer tracings obtained from the same patient. A center forms rhythmic stimuli in an interval of approximately 135 to 140 (42 beats per minute) and all stimuli sent out by this center which appear outside the refractory phase of a sinus beat cause an extra contraction. On the basis of this interpretation the sixth beat in Lead I of Fig. 1 represents a normal sinus beat whose P wave occurs at its normal time and is buried in the preceding QRS complex. It is not due to an extrasystole. The fifth systole in Lead I is caused by a parasystolic, ectopic stimulus and is interpolated between two normal sinus beats.

Of interest is the observation that in this tracing the form of the parasystolic beats is the same as that of the sinus beats. Only sinus beats shortly after a parasystolic beat and vice versa look abnormal due to aberrant intraventricular conduction. One may assume therefore that the parasystolic focus is situated in the auriculoventricular node or in the common part of the auriculoventricular bundle above the bifurcation.

The study of other tracings confirms the diagnosis of a parasystole due to interference of two rhythms. Figure 2 represents one tracing, which, for the purpose of reproduction, was cut into four strips. No part of the tracing is omitted. The rate of the sinus beats is 68 to 70 per minute. The second ventricular complex of the first strip in Fig. 2 is premature and so is the fifth ventricular complex. The distance between these two beats measures 258. The same interval, with variations of only a few hundredths of a second is measured between all the other abnormal beats in this tracing. One sees the heterotopic rhythm is independent of the sinus rhythm and the abnormal beats appear at different times during diastole. At the end of the first strip one parasystolic beat is interpolated between two normal beats; in all other instances the appearance of a parasystolic beat blocks one sinus beat. From the analysis of the tracing in Fig. 1 one can safely assume that the period of 258 does not represent the actual interval of the stimuli formed by the abnormal focus; rather this measures only half of this value, that is 129 (46 beats per minute). Measurement readily reveals that every second stimulus formed by the parasystolic focus appears during the refractory phase of a sinus beat so that it could not elicit a response. The manifest length of the period of the parasystolic focus therefore represents twice the value of the actual one.

During an observation period of five months the parasystole was constantly present. Five and one-half months after the patient was first seen the electrocardiogram showed only occasional isolated ventricular extrasystoles with fixed coupling, with the same form as the parasystolic beats.

Figure 3 shows interesting variations of the parasystolic arrhythmia observed in this patient. In the tracing of Fig. 3,*A* a sinus rhythm exists with a period of about 90 and a P-R distance of 42 to 43. The second, fifth, ninth, and twelfth ventricular systoles represent parasystolic contractions. The three intervals between these beats measure: 267, 275, and 267. Here again, one must assume that the real automatic period measures only one-half of these long diastoles, that is, about 135. Remarkable is the increased length of the interval between the interpolated parasystolic beat (fifth ventricular systole) and the following parasystolic beat. The cause of this lengthening will be discussed later.

Figure 3,*B* reproduces a sinus rhythm with periods varying between 76 and 80 and P-R intervals of 43. The second, fourth, eighth, thirteenth, and sixteenth ventricular beats are due to parasystole. The distances between the parasystolic beats measure: 124, 264 (124×2 plus 16), 383 (124×3 plus 12) and 248 (124×2). Here, too, the distance between the interpolated ectopic beats and the following ectopic beats is longer than expected.

Whenever the opportunity was afforded to measure the ectopic, parasystolic period, for example, the distance between the second and the fourth QRS complex in Fig. 3,*B*, they were always identical in the same tracing.

Discussion: One of the important criteria for the diagnosis of parasystole is the presence of combination beats. If two rhythms interfere with each other due to the activity of two independent foci, occasionally stimuli may be formed more or less simultaneously by both. The ventricle is then activated in part by one and in part by the other stimulus. The resultant ventricular complexes show all variations between those of the sinus rhythm and those of the ectopic, parasystolic beats. In Case 1 combination beats were not found. This must be expected because of the site of stimulus formation of the parasystolic focus, above the bifurcation of the auriculoventricular bundle. The QRS complexes of the sinus as well as ectopic rhythms look alike because impulses starting in either center had to use the same path before reaching the ventricles and one could not follow the other before the tissue recovered from the preceding conduction. An ectopic stimulus could not be conducted from the parasystolic focus simultaneously with a sinus stimulus.

In the analysis of the tracings of Fig. 3 it was pointed out that some intervals were a little longer than usual. In the many tracings taken from this patient, longer intervals like that between the 13th and the 16th beat of Fig. 3,*B* were always a simple multiple of the short parasystolic interval such as measured between the second and the fourth ventricular complex in Fig. 3,*B*. Some intervals, however, were definitely longer.

Exceptions to the rule of the least common denominator in parasystole occur and they may have various explanations.[10] The abnormal parasystolic focus may work arrhythmically owing to a change of nerve tonus. Arrhythmias in a center forming stimuli at a slow rate often are greater than in a center with a fast rate. The possibility that some stimuli are conducted with delay from their focus to the ventricles also merits consideration. If this were the case, however, the parasystolic beats appearing early in diastole would most likely be conducted with some delay. Actually in the tracings of Case 1, these periods were always of the length expected and the following one was longer than one might anticipate.

Study of the tracings illustrated in Fig. 3 reveals that usually those periods were longer in which a parasystolic beat was preceded by a sinus P wave at a short distance, where, in other words, one was justified in assuming that a normal stimulus passed the parasystolic focus shortly after it had sent out a stimulus; usually this parasystolic beat is interpolated because the P wave of the sinus beat appearing just before the ectopic beat reaches the ventricles with some delay.

The most probable explanation for the prolongation of these intervals seems the following one: the parasystolic center is protectively blocked. This protective block should not be understood as an area of unidirectional block surrounding the ectopic center; rather the ectopic center is unable to respond to the normal stimuli spreading over the heart either because the stimuli are below the threshold or because the center is less excitable.[2] The absence of a response to conducted stimuli enables the center to form stimuli of its own. During the repolarization period changes take place in the cell membrane, which, under certain conditions, lead to the appearance of the phenomenon of a supernormal phase of excitability. During this phase which coincides with and is related to

the negative after-potential the cell may become more excitable to conducted stimuli. This temporarily abolishes the "protective block" and permits conducted sinus stimuli to break into the ectopic center, delaying its stimulus formation for a few hundredths of a second. Thus, whenever the sinus stimulus arrives at the right time, that is during the supernormal phase, it reaches the ectopic center; this would explain why only those ectopic periods were longer in which a P wave preceded the ectopic beat at a certain distance.

Consequently, this case shows a parasystolic rhythm due to the activity of an ectopic center above the bifurcation of the bundle and periodic disturbances of the ectopic rhythm due to a break in the "protective block."

CASE 2.—L. T., a 24-year-old Negro woman complained of shortness of breath on exertion for ten years. Dyspnea at rest and orthopnea were present for two years. The examination revealed a rheumatic stenosis and insufficiency of the mitral and aortic valves. During four years of observation congestive cardiac failure recurred at ever shorter intervals and the response of the patient to digitalis, mercurial diuretics and sodium-poor diet became progressively less satisfactory. In the final stage of the illness auricular flutter with rapid ventricular action appeared. This necessitated the administration of large doses of digitalis which abolished the arrhythmias which will be described presently.

Electrocardiograms: The electrocardiogram of the sinus beats shows large and slurred P waves in Leads I and II (Fig. 4). They are widened to 0.12 second. Presumably this widening of the P waves accounted for a P-R interval measuring 0.20 second. The T waves, abnormally low in Leads I and II, are inverted in Lead III. In CF_4 the QRS complex shows a high R wave without S wave. The RS-T segment as well as the T wave are depressed below the base line. All these changes are common in combined lesions of the mitral and aortic valves with hypertrophy of the left ventricle. The rate is approximately 80 per minute. No drugs had been administered when this tracing was obtained.

The sinus rhythm is interrupted by abnormal ventricular complexes which appear in groups of two of five, most frequently of four. Between these abnormal beats at least one sinus beat is always found. The first, and often also the second, abnormal beat always appears approximately at the time a normal sinus beat is due. Therefore the ventricular complex usually is altered and one may assume that a large part of the ventricles is activated by the sinus stimulus and a small part by the abnormal stimulus originating in the ventricular focus (combination beat). Thus the third and the fifth ventricular complexes of Lead I in Fig. 4 show slight but definite changes due to the dual activation of the ventricles. The abnormal beats appearing later show more clearly a form which must be expected with an abnormal site of stimulus formation in the ventricles. Measurement of the distances between the abnormal beats of each group in each lead shows fairly constant values. Thus, in Lead I of Fig. 4 we measure 149, 146, 144, 146, 144; in Lead II the distances measure 145 and 142; in Lead III they are 148, 144 and 144; finally in the chest lead they measure 147 and 144. The values of the first abnormal periods are inexact because the presence of combination beats does not permit accurate timing of the appearance of the abnormal stimulus. The first abnormal beat of each series appears when the normal sinus beat is spreading over the ventricles. It seems safe to assume that the ectopic stimulus appears a few hundredths of a second after the beginning of the QRS complex. Therefore the first intervals of each group are a little shorter than those given above and the third (sometimes the second) is a little longer. One gains the impression from this tracing that an automatic ventricular center periodically was awakened for a short time and formed about 42 stimuli per minute. This center works rhythmically. It is not influenced by the sinus beats and is protectively blocked.

The twelfth beat in Lead III and the tenth in the chest lead have a different form and must be attributed to simple ventricular extrasystoles unrelated to the disturbance analyzed in the preceding paragraphs.

We were able to register an electrocardiogram of this patient four years before that of Fig. 4 was obtained. At that time (Fig. 5) the rate of the sinus beats was slower and amounted to 66

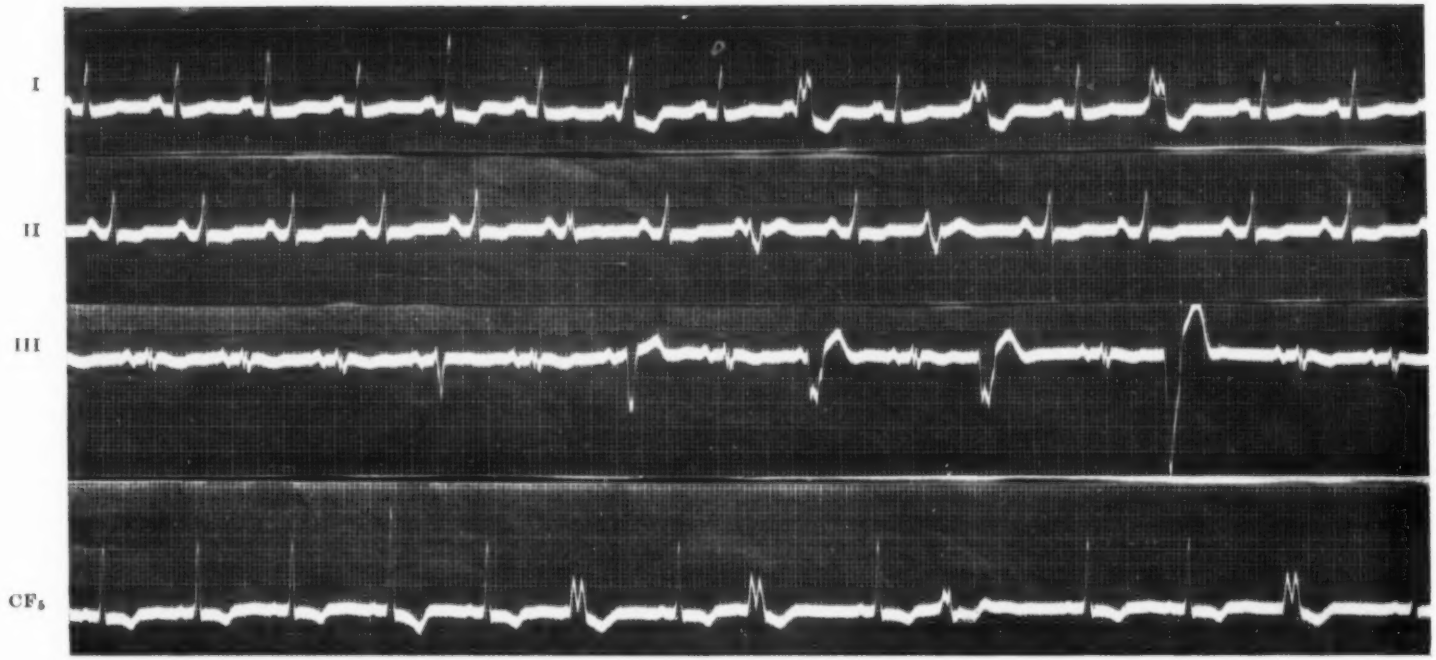

Fig. 4.—Three standard leads and CF_5 of Case 2 showing intermittent parasystole.

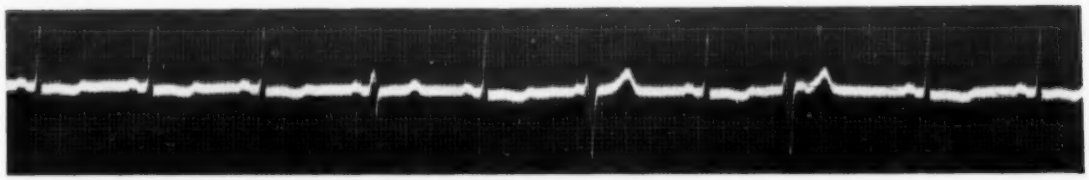

Fig. 5.—A slower sinus rhythm (Case 2) coincides with a slower parasystolic rhythm.

beats per minute, the diastoles being 90. In this tracing three abnormal beats appear, the first again as a combination beat with a P-R distance of 0.17 second. The intervals between the abnormal beats measure 175 and 165. Thus, a comparison of Fig. 4 and Fig. 5 suggests that with a more rapid sinus rhythm at different periods of observation, the rate of the ectopic rhythm also differed. With a sinus rate of 80 the automatic rate was 41 (Fig. 4). With a sinus rate of 66 in Fig. 5 the ectopic rhythm has a rate of only 35.

Of interest, and peculiar to this patient, is the observation that a new series of abnormal beats started only when the first ectopic beat appeared so late in diastole that it coincided more or less with a normal sinus beat spreading over the ventricles. When abnormal beats appeared earlier in diastole they remained isolated and were not followed by others.

Sometimes as many as 80 regular sinus beats appeared between the single groups of ectopic beats. In all tracings it is obvious that ectopic beats could have appeared easily in the long diastoles but are absent. Consequently, one may assume that after forming 2 to 6 stimuli the ectopic, automatic center stopped its activity. Any new ectopic stimulus however, coming at the right time late in diastole, when a normal stimulus is due, elicits a new short series of ectopic beats.

The constancy of the distance between the first ectopic beat of each series and its preceding normal beat is astounding. Thus in the strip from which Fig. 4 was obtained five out of seven series of abnormal beats begin 0.76 second after a normal beat. One may speak of a constant coupling of the first beat of a series. A corollary of this fact is the constancy of the P-R distance of these first beats as evident from the tracings.

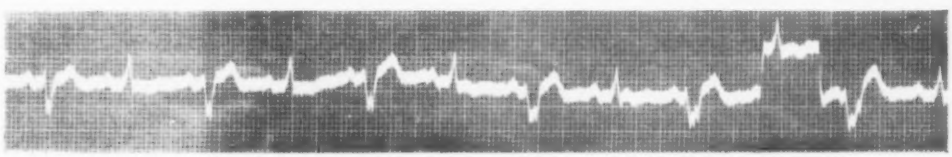

Fig. 6.—Continuous parasystole in Case 2 (Lead III).

In Fig. 6 (Lead III) which was obtained from this patient on another occasion superficial inspection seems to reveal a ventricular bigeminy. Closer analysis shows, however, that the abnormal ventricular beats gradually move closer to the preceding beat so that the P-R distance shortens. The abnormal ectopic complexes gradually widen. The distance between the abnormal ventricular complexes constantly measures 131. Therefore, we may assume that we are dealing with a parasystolic mechanism with a ventricular center constantly and independently forming stimuli with a rate of 45 per minute. At the beginning of Fig. 6 a larger, and at the end a smaller, part of the ventricles is activated by the sinus stimulus while the rest is activated by the ectopic stimulus. The slowness of this interference of both rhythms, the sinus and the ectopic rhythm, is due to the fact that two sinus periods measure 132, while one parasystolic period measures 131. The tracing may be compared with some cases of complete auriculoventricular block where two auricular periods are about equal to one automatic period of the ventricles. If this is the case, the P-R interval changes only very gradually and long tracings must be taken in order to differentiate from 2:1 and complete auriculoventricular block. This disturbance of rhythm was registered only in Lead III and was absent in the others.

Discussion: The constant intervals between the abnormal beats of each group, the appearance of combination beats and finally the tracing of Fig. 6 demonstrate the existence of parasystole. This case possesses some features which are not found in the classic picture of parasystole. The parasystolic mechanism, the formation of rhythmic ectopic stimuli stops after a few beats are formed. We are dealing with an "intermittent parasystole,"[5] a periodic awakening and vanishing of an active ventricular center, which is not disturbed by the sinus

stimuli. Another unusual observation is the fact that every group of automatic beats begins in a given tracing at a definite interval after the P wave or rather after the previous sinus beat so that the first ectopic beat of each series always appears when a normal stimulus spreads over the heart.

It has been observed before that parasystole changes into a bigeminy with fixed coupling of the extrasystoles without any change of form of the abnormal beats.[8,12] Such rare instances were attributed to a change of status in the abnormal center, abolishing its protective block and leading to an extrasystolic stimulus formation whenever a sinus stimulus spreads over the ventricle. Here, however, short periods of parasystole always begin with a fixed coupling of the first ectopic beat to the preceding sinus beat. Sometimes the extra stimulus is formed after, sometimes shortly before the normal stimulus spreads over the ventricle. The latter mechanism is demonstrated by the slightly shortened P-R interval of these abnormal beats and the abnormal form of the first part of the QRS complex.

It is difficult to assume that a normal sinus beat spreading over the heart elicits an abnormal stimulus formation in a center which it has not as yet reached. Therefore, one is forced to postulate that the first abnormal beat of each series is formed in some way by the last preceding sinus beat to which it is coupled. This ectopic beat, appearing late in diastole when the next sinus beat is due, is followed by a short series of parasystolic beats. After each extrasystole arriving late the ectopic center temporarily experiences a change of excitability so that it is not affected by conducted sinus stimuli; it becomes protectively blocked and this must lead to an independent stimulus formation in this center, a parasystole. Why only extrasystoles appearing very late in diastole induce this mechanism to difficult to explain and any discussion at this time would be purely speculative.

CASE 3.—A 54-year-old woman came to the clinic because of dizziness and occasional palpitation. There was no history of any previous illness. Examination revealed a heart of normal size and shape and a slight accentuation of the second aortic sound. There was a soft systolic aortic murmur. The blood pressure was 160/110 mm. of mercury. During an observation period of 15 months, thirty-four electrocardiograms were taken. They showed invariably, with the exception of a period during which the patient received digitalis for experimental reasons, an unusual disturbance of rhythm. The analysis of the tracings with the time marker indicating 0.05 second, will proceed from the simplest to the more complicated ones.

Electrocardiograms: Fig. 7,*A* shows a regular sinus rhythm with a rate of 69 beats per minute (Lead II). The P-R interval of the sinus beats measures 0.16 second. Following every second sinus beat, two abnormal beats are visible. The distance between the first abnormal beat and the preceding normal one in the three groups of Fig. 7,*A* measures 44. The first abnormal beat of each group undoubtedly represents a ventricular extrasystole of the common variety with fixed coupling. It is more difficult to establish the nature of the second abnormal beat of each group. It could represent a second ventricular extrasystole. Another possibility would be an aberrant conduction of a sinus beat. With this interpretation the sinus beats after the extrasysoles might be aberrantly conducted within the ventricles since they appear early in the recovery period. Aberrant conduction of the sinus beat following interpolated ventricular extrasystoles is known to occur. We favor the second interpretation because: a) the fixation of the second abnormal beat to the first one is not constant; the distances between the two abnormal beats measure 44, 47 and 53. Such variations are unusual in ventricular extrasystoles but they do occur. Furthermore, b) the form of the second abnormal beat changes with the change of interval, the ventricular complex having a less abnormal appearance with an increase of length of the preceding

diastole. The second abnormal complex of the third group in Fig. 7,*A* appears after the longest diastole and shows the least aberration. Further arguments in favor of this interpretation will follow.

In Fig. 7,*B* and *C* another disturbance of rhythm appears. Figure 7,*B* reproduces Lead I, Fig. 7,*C*, Leads II and III. Normal sinus beats are visible in the beginning and the center of Lead I. They are followed at a distance of 41 by abnormal beats. The pauses between the abnormal beats constantly measure 72. Lead II shows only this ectopic rhythm. Lead III shows three sinus beats which are followed after a diastole of 41 by three ectopic beats with diastoles of 72. The sinus rate is 72, the rate of the ectopic rhythm is 82. It is remarkable, that the first of a series of ectopic rhythm shows constant coupling, that is, always the same distance from the preceding sinus beat.

A similar series of automatic beats is shown in Fig. 7,*D*, toward the end of the tracing. Here the sinus periods measure 70. The second sinus beat in the second half of the tracing is followed after a diastole of 42 by an ectopic beat and the following diastoles between ectopic beats measure 75 and 76. In some of the tracings collected from this patient up to sixty automatic ectopic beats follow each other with a constant length of diastole. The question arises what is the auricle doing during the presence of long chains of ectopic rhythm? In no tracing were negative P waves visible in Leads II and III so that a reversed conduction of the ectopic beats to the auricle can be discarded. It is more probable that the sinus rhythm continued undisturbed in the auricles and the normal P waves were invisible because they were buried in the QRS-T complexes. This phenomenon was possible since the sinus and ectopic rhythms had approximately the same rate.

In this patient we are dealing again with an ectopic stimulus formation in the ventricles in which the coupling of the first of a series of ectopic beats to the preceding normal sinus beat is constant.

More complicated, but very common in this patient was the disturbance of rhythm which appears in the first half of Fig. 7,*D*. Two normal sinus beats are followed by seven abnormal ventricular complexes appearing for the most part in groups of two. The first abnormal beat is separated from the preceding sinus beat by an interval of 42. The interpretation of this arrhythmia as a group of extrasystoles, or extrasystoles with alternation of cycle length[7] is improbable. More probable, and borne out by further analysis of the tracings, is the assumption that we are dealing with a combination of the disturbances previously discussed, that is, aberrantly conducted beats from the auricle and automatic beats from an ectopic ventricular center. The automatic beats are not disturbed by the sinus beats. In this interpretation the second sinus beat of Fig. 7,*D* is followed by four abnormal ectopic beats (the first, third, fifth, and seventh abnormal beats). The first comes after a coupling of 42. The second, fourth, and sixth abnormal beats represent aberrantly conducted normal sinus beats. If one measures the distances between the first and third, the third and fifth, and the fifth and seventh abnormal beats, the distances are 75, 76, and 77, respectively. These values correspond to those measured in the second half of the same tracing in which abnormal heterotopic beats appear alone, and undisturbed by sinus beats. If the distance between an ectopic beat and the following sinus beat is short, the succeeding diastole is that much longer. The pauses are compensatory. Since the formation of ectopic stimuli proceeds rhythmically, without disturbance by the sinus beats, a "protective block" exists and we are dealing once again with an intermittent parasystole.

Two tracings of Fig. 8, selected from other long strips, confirm this explanation and demonstrate that we are dealing with aberrantly conducted sinus beats between the ectopic beats and not with ventricular extrasystoles.

In Fig. 8,*A* the sinus rhythm has diastoles of 90 (rate of 66 per minute); in the first two groups the sinus rhythm is followed by an extrasystole after 0.44 second. Following diastoles of 50 and 51, respectively, an abnormal beat appears which is clearly conducted from the auricle. Due to the slower rate of the sinus rhythm in this tracing the normal P wave preceding the sinus beats is unmistakeable after the T wave of the extrasystole. The third sinus beat is followed by a series of six abnormal beats the first again appearing after an interval of 44. The diastoles between the abnormal beats measure: 45, 50, 43, 51, and 42. The distances between the first and third, the third and the fifth abnormal beats measure, therefore, 95 and 96, respectively, and the pauses are compensatory.

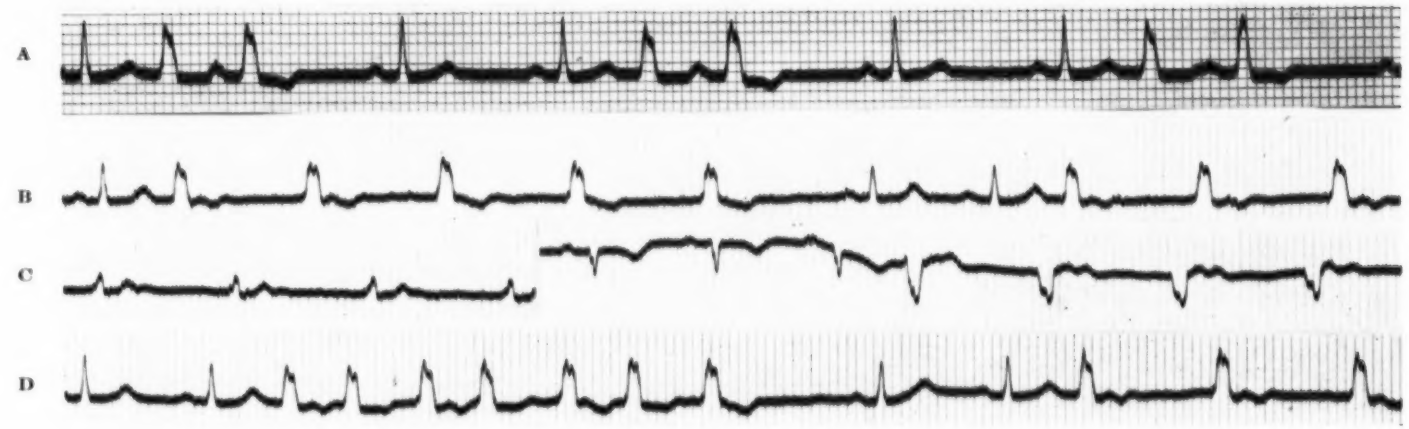

Fig. 7.—The top tracing (*A*) shows interpolated ventricular extrasystoles with unusual aberration of the first post-extrasystolic beat; *B* and *C* show the three standard leads with intermittent parasystole; *D* shows a combination of the disturbances in *A*, *B* and *C*.

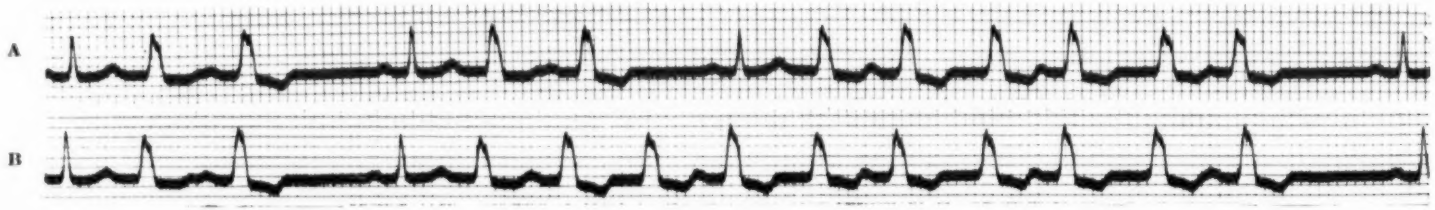

Fig. 8. Intermittent parasystole and aberrant conduction of sinus beats.

Figure 8,*B* was obtained on another day when the sinus period was 100 (60 beats per minute). At its beginning a group appears similar to the beginning of Fig. 8,*A*. Owing to the slower rate of the sinus rhythm the P wave appears late after the T wave of the extrasystole ends and the aberrantly conducted sinus beat appearing after 0.52 second, shows less abnormality. The second sinus beat in Fig. 8,*B* is followed by a series of ten abnormal beats. The first of the series resembles the extrasystole at the beginning of Fig. 8,*B* after a diastole of 43. The following intervals measure: 47, 46, 45, 48, 43, 51, and 50. The distances between the automatic beats have a length of 93, 93, 93, and 94. As in all other tracings the reciprocal values of the length of the succeeding diastoles are evident and confirm the interpretation given.

Still more complicated tracings like Fig. 9 are now more easily analyzed. In Fig. 9 the rhythmic activity of an automatic center causes the first, third, fifth, seventh, eighth, and ninth systoles. The distances between these ectopic beats measure: 82, 83, 80, and 80. Between these ectopic automatic beats, three conducted sinus beats appear. The aberration of the first two, coming late in diastole is slight, while the third one, between the third and fifth ectopic beat, is markedly aberrant.

During the period in which the heart was under the influence of digitalis no parasystole was observed. The latter returned shortly after digitalis was discontinued.

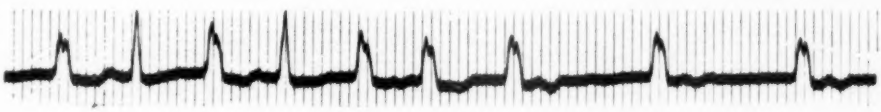

Fig. 9.—Description in text.

Discussion: In this subject again a parasystolic center exists in the ventricle forming rhythmic and independent stimuli. The center is not disturbed by sinus beats. As in the second subject, parasystole always started with a beat which constantly shows fixed coupling to the preceding sinus beat. This is another example in which an intermittent parasystole is awakened periodically and disappears. Combination beats were not observed but they were not expected because of the type of interference of the two rhythms. The fixed coupling and the rate of sinus rhythm and ectopic rhythms, respectively, permit an interpolation of a sinus beat between two automatic beats and no combination beats occur. The ectopic rhythm stopped after a while but the chains of ectopic beats were in general longer than in Case 2. When single ectopic beats appeared (Fig. 7,*A*) one had the impression of simple extrasystoles. The series of ectopic beats never started unless the first of the series was coupled to the preceding beat.

GENERAL DISCUSSION

The three instance of parasystole discussed in this paper show unusual features. In the first subject the focus of the ectopic stimulus formation is situated above the bifurcation of the A-V bundle. Usually it is found in deeper parts of the ventricles and rarely in the auricle. The break in the protection of the center whenever it is reached by another stimulus early in diastole is another unusual finding in this patient. A supernormal phase of excitability is assumed to cause this phenomenon. It is reemphasized that the protection of the ectopic center need not be caused by a conduction disturbance such as a unidirectional block zone surrounding this center. Diminished excitability of a center to

conducted stimuli adequately explains the phenomenon.[2] Consequently, the terms "protective block" or "entrance block" are misnomers since we are not dealing with a block, a disturbance of conduction. We propose to speak of "protection" of the ectopic parasystolic center instead of "protective block."

In Cases 2 and 3 intermittent parasystole is represented. A parasystole with protection of the ectopic center appears and disappears after a short time and it is important that the first ectopic beat of each series is bound to a sinus beat with fixed coupling; in other words, it is elicited in some way by this beat. Thus we have independent, automatic (parasystolic) and dependent, forced (extrasystolic) stimulus formation originating in the same center within a few seconds.

Case 3 is also interesting because many ectopic beats are interpolated (as in Case 1); moreover the first post-ectopic beat assumes the form of the ectopic beat. One might expect that whenever an interpolated extrasystole originates in the right ventricle it spreads over the right bundle branch first and then over the left. Therefore, the right bundle branch should recover first and the next post-extrasystolic beat in interpolated extrasystoles should spread over the right bundle branch first and should (as in Case 3) have the same form as the extrasystole. One would expect this to be the rule but actually it is the exception for the reason given by Ashman.[1] The delay experienced by the first post-extrasystolic beat after interpolated extrasystoles in the auriculoventricular bundle above the bifurcation is sufficient to permit the tissue below the bifurcation to recover sufficiently. Therefore, abnormal intraventricular conduction is not too common for the first beat after an interpolated ventricular extrasystole.

Of interest are the parallel variations of the sinus and the ectopic rates in Case 2. An increase of rate of one rhythm is accompanied by an increase of the other and vice versa. These variations did not escape the early observers of parasystole[4] but they are rarely as pronounced and consistent as in this subject. Neurogenic, hormonal, electrolyte influences simultaneously affect both centers.

In Case 1 the break in the protection of both centers leads to a connection between both rhythms and permits, as in interference with dissociation, the same pattern to appear again and again in the electrocardiogram. In a different way the fixed coupling of the first of a series of automatic beat and the relatively short duration of each series in Cases 2 and 3 lead to repetition of the same pattern.

Cases 2 and 3 which show extrasystolic and automatic stimulus formation originating in the same center in a continuous change are particularly interesting because they represent as far as we know the first known cases showing this disturbance in this form. Nevertheless, a sharp separation of parasystolic and extrasystolic stimulus formation is necessary.[6] In parasystole we are dealing with an automatic independent formation of stimuli. An extrasystole represents a dependent stimulus formation, since it is always caused in some way by the preceding beat to which it is coupled.

It has been pointed out before[2,3] that parasystole usually develops in an abnormal heart. The cases reported in the present paper are no exception. It is, however, possible that these disturbances are occasionally caused by a micro-

scopic abnormality of the heart, that is, a lesion in "a center." Therefore, occasionally, parasystole is found in an apparently healthy heart. An instance of parasystole recently reported by Vedoya and his associates[11] seems to represent such an observation.

SUMMARY

Three cases of parasystole with simple interference of two rhythms showing unusual features are described.

In the first case the ectopic center was situated in the auriculoventricular bundle above the bifurcation. Combination beats were absent. Both rhythms were occasionally united when the protection of the ectopic center towards normal sinus stimuli disappeared. This phenomenon is explained by a supernormal phase of excitability of the ectopic center.

The two other observations concern "intermittent parasystole" in which an ectopic center periodically appears and disappears. The first ectopic beat of each series is coupled to the preceding sinus beat and apparently elicited by the latter. Case 2 shows a parallel variation of the sinus rate and the rate of the ectopic center. Case 3 shows an interesting intraventricular disturbance of conduction following interpolated beats.

It is emphasized that the term "protective block" is not applicable because we are not dealing with a zone of unidirectional block. The protection of the ectopic center against conducted stimuli is fully explained by its diminished excitability. Periodic changes of this excitability may cause the appearance and disappearance of parasystole.

All three observations show temporary disappearance of the protection of a parasystolic center. This leads to hitherto unknown disturbances of rhythm and permits a better understanding of the mechanism of parasystole.

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ACUTE COR PULMONALE IN THE ABSENCE OF PULMONARY EMBOLISM

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SINCE the classic paper of McGinn and White[1] appeared in 1935, the diagnosis of pulmonary embolism is usually made whenever the clinical and electrocardiographic pattern of acute cor pulmonale presents itself. However, the terms acute cor pulmonale and acute pulmonary embolism too often have been used interchangeably. It is not appreciated sufficiently that there may be causes or precipitating factors of acute cor pulmonale other than pulmonary embolism. The changes occurring with pulmonary embolism may be reproduced by any mechanism leading to a sudden marked increase in the resistance against which the right ventricle must work. The purpose of this report is to cite examples of acute cor pulmonale with typical electrocardiographic changes in which pulmonary embolism was either absent or insufficient to explain the clinical picture.

Originally, as the selection of the term "acute cor pulmonale" implies, the disturbed physiology, the clinical picture, and the electrocardiographic changes were considered primarily a reflection of the dilatation of the right ventricle resulting from the increased burden imposed upon this chamber.[1] Now it is realized that the additional factor of myocardial ischemia, especially of the right ventricle and posterior wall of the left ventricle, is of equal importance.[2-6]

A brief review of the complex functional alterations which contribute to this state is presented in order to understand how other conditions can lead to acute cor pulmonale.

CAUSE OF RIGHT-SIDED DILATATION OF THE HEART WITH CLOCKWISE ROTATION IN ACUTE COR PULMONALE

In normal hearts the pressure in the main pulmonary artery changes little, even with exercise, as compared with that occurring simultaneously in the aorta.[7-9] But, the sudden increase in resistance to blood flow in the pulmonary circuit in acute cor pulmonale, with the associated marked pulmonary hypertension, tends to increase the demands on the right ventricle to such an extent that dilatation of this chamber occurs with concomitant clockwise rotation of the heart on its longitudinal axis. The deep S waves in Leads I and II in the absence of right bundle branch system block may be considered manifestations of this dilatation and clockwise rotation.[1,10]

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CAUSES OF MYOCARDIAL ISCHEMIA IN ACUTE COR PULMONALE

1. *Reduced coronary flow.*—The reduction in the coronary arterial flow is due to several factors.

a.) The increased pressures within the right ventricle and atrium, by interfering with the drainage from the Thebesian vessels and the coronary sinus, reduce the effective pressure gradient between the coronary arteries and their drainage systems. The associated increased intramural pressure of the right ventricle further impedes coronary blood flow. Since this reduction of blood flow is most marked in the right coronary artery, the evidence of myocardial ischemia is most marked in the right ventricle and the posterior portion of the left ventricle.[11-13]

b.) The diminished output of the left ventricle as a result of the obstruction to blood flow in the pulmonary circuit (eventually reflected in a fall of systemic blood pressure and peripheral circulatory collapse) decreases further the effective pressure gradient between the coronary arteries and their drainage systems.[14-17] In addition, the diminished cardiac output per se decreases coronary flow.[17]

c.) Although initially of compensatory value and usually present in acute cor pulmonale, as a result of both reflex and chemical factors, tachycardia may lead ultimately to a further reduction in cardiac output and so, secondarily, to a diminution of the coronary flow by encroaching upon the rapid inflow phase of the heart.

d.) Various reflexes which directly diminish coronary blood flow in acute cor pulmonale have also been described. The evidence for so-called pulmonocoronary reflexes in which reflex vagal coronary vasoconstriction is allegedly produced by the sudden obstruction to flow in the pulmonary arteries[20] has not been confirmed by recent experiments.[4,21] The pulmono-pulmonary reflex in which pulmonary emboli are accompanied by a reflex vasoconstriction of other branches of the pulmonary arteries without intraluminal obstruction appears more likely since it parallels the situation so frequently seen in embolization of major peripheral arteries and has been demonstrated experimentally.[4,22] Acute hypoxemia has been shown to be associated with an increase in pressure in the main pulmonary artery and has been assumed to result from pulmonary arteriolar constriction.[18] Peripheral circulatory collapse which may follow acute cor pulmonale has been shown to produce pulmonary edema which would lead to acute hypoxemia and also act to increase resistance to blood flow through the lung.[19]

2. *Diminished oxygenation of blood flowing through lungs.*—In acute cor pulmonale, and particularly in the special cases considered in this report, impairment of pulmonary function by intrinsic pulmonary disease leads to diminished oxygenation of the blood circulating through the lungs. In addition, the rapid shallow breathing often present in such patients also makes for inefficient ventilation and may thus further contribute to the hypoxemia.

3. *Increased oxygen requirement of the heart as a result of its increased work.*—The work of the heart in acute cor pulmonale must increase in order to overcome the greater resistance in the pulmonary circuit. Tachycardia may also further

tax the heart. Since the oxygen requirement of heart muscle increases at least in proportion to the amount of work performed and the degree of dilatation,[23,24] the relative ischemia is further aggravated in the presence of a diminishing supply of oxygen to the heart. Significant fever, while unusual as an early manifestation of acute cor pulmonale due to embolism, was present in our two patients and thus tended to increase the oxygen requirements of the peripheral tissues as well as of the heart.

It is the ultimate inability of the heart to meet these increased demands for work in the presence of relative ischemia that eventually results in failure and death in acute cor pulmonale.

ELECTROCARDIOGRAPHIC CHANGES

Of the electrocardiographic changes found in acute cor pulmonale the following specific changes may be considered as resulting from myocardial ischemia, especially of the right ventricle and the posterior wall of the left ventricle:

1. Development of depression of the S-T segment in Leads I, II, V_5 and V_6 (staircase variety).

2. Inversion of the T wave in the precordial leads from the right half of the precordium (V_2-V_4). When inversion is limited to V_2, it may be due to extreme clockwise rotation of the heart; however, when present in leads farther to the left, myocardial ischemia is the more likely cause.

3. Development of a Q_3 with T_3 inversion. In Lead aV_F in acute cor pulmonale, a Q wave may be present and tiny (vertical position of heart), or absent (semihorizontal position of heart). In the latter case, the Q_3T_3 pattern is due to the fact that R and T are upright and taller in aV_L than in aV_F. Lead III which is roughly equivalent to $(aV_F - aV_L) \times 2/3$ will as a consequence show a Q and an inverted T.[25] Whether the reduction in amplitude of R and T in aV_F is partially due to severe ischemia of the diaphragmatic surface of the heart or is merely a result of change of the heart's position remains to be established.

4. Development of right bundle branch system block, complete or incomplete. This frequently occurs very early after the onset of the acute cor pulmonale and may later disappear only to reappear terminally,[26,27] but occasionally the right bundle branch system block may persist from onset to death or recovery. This intraventricular block is due to hypoxemia of the right ventricle as a result of the inadequate coronary oxygen supply and the increased work, or of the mechanical effect of the sudden massive dilatation of the right ventricle.

5. Arrhythmias. They are frequently found. They may be produced reflexly and hence are neurogenic in origin. They may also be due to ischemia of the myocardium leading to areas which act as ectopic foci for the origin of ectopic rhythms[28] or to areas in which conduction is critically slowed to permit the development of re-entry mechanisms which then are responsible for the arrhythmias.[29,30]

CASE REPORTS

The following case reports demonstrate that a sudden increase in the resistance in the pulmonary vascular circuit, especially when associated with a con-

comitant, sudden diminution in the reserve of the right ventricle, can lead to the clinical and electrocardiographic picture of acute cor pulmonale in a patient in whom the right ventricle has been laboring under increased strain for some time.

CASE 1.—P. J., a 36-year-old Negro woman, entered Michael Reese Hospital on Dec. 1, 1948, because of a constant, nonproductive cough with hemoptysis, and pain in the left chest and shoulder. The significant findings were as follows: The left eye showed slight miosis, enophthalmos, and ptosis of the eyelid. A hard mass measuring 2 × 2 cm. was palpable in the left supraclavicular region. Examination of the chest revealed dullness with slight diminution of the breath sounds in the upper third of the left side of the chest posteriorly and anteriorly. There was

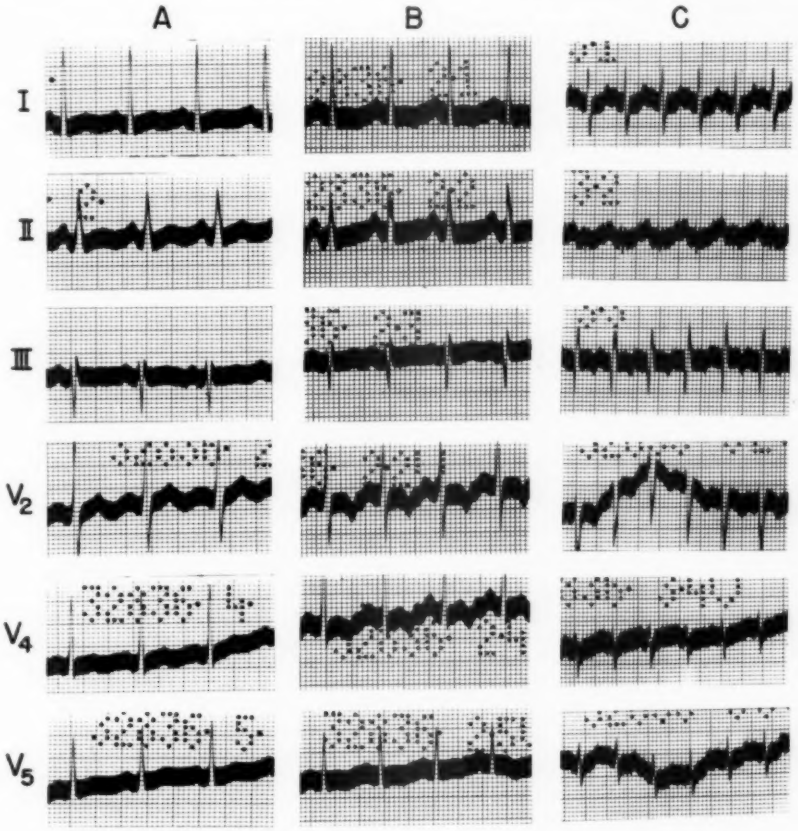

Fig. 1.—Electrocardiogram of Case 1. A. Dec. 2, 1948 (thirty-one days before death). B. Dec. 24, 1948 (nine days before death). C. Jan. 3, 1949 (twenty-four hours before death). Discussed in text.

dullness with absent diaphragmatic excursions in the left base posteriorly. Examination of the heart revealed the second heart sound over the pulmonic area to be louder than over the aortic area. The blood pressure was 120/80 mm. Hg. No murmurs were heard. Abdominal examination was essentially normal. On pelvic examination, the right ovary was felt to be 6 × 6 cm. in size, hard and fixed.

Laboratory examinations: X-rays and fluoroscopy of the chest showed a dense infiltration extending from the upper mediastinum into the left upper lung field with partial atelectasis of the left upper lobe and a shift of the trachea to the right. The left side of the diaphragm was elevated

and exhibited paradoxical motion with respiration. X-ray examination of the entire gastrointestinal tract was negative except for the nonvisualization of the gall bladder. Intravenous pyelograms were likewise negative. Admission blood studies, blood chemistry, urinalysis, sputum examinations and culture were noncontributory. Cytological examination of the bronchial washings obtained by bronchial lavage revealed squamous epithelial cells, occasional polymorphonuclear leucocytes, and lymphocytes. No cells typical of neoplasm were seen. Decholin arm-to-tongue circulation time was 14 seconds. An electrocardiogram taken on Dec. 2, 1948 (Fig. 1,*A*) showed a left axis shift, and T was abnormally small in Lead I.

Hospital course: A biopsy of the left supraclavicular mass revealed metastatic carcinoma simplex. The patient lost ground rapidly while in the hospital. Two weeks after admission her liver became palpable and slightly tender. It continued to increase in size so that at the time of death the liver edge was felt 7 cm. below the right costal margin. At no time was peripheral edema present. An electrocardiogram (Fig. 1,*B*) taken on Dec. 24, 1948 (9 days before death), now showed slight S-T depression in Leads I and II; the T wave in Lead I was inverted, the T wave in Lead II was not discernible, and T waves were inverted in all the chest leads. Serial chest roentgenograms showed progressive atelectasis of the left upper lobe with increasing pleural effusion in the left pleural space and small patchy areas of increased density in the left lower lung field and in the right lung (Fig. 2). Her red blood cell count fell to 3.7 million and hemoglobin to 10.2 grams.

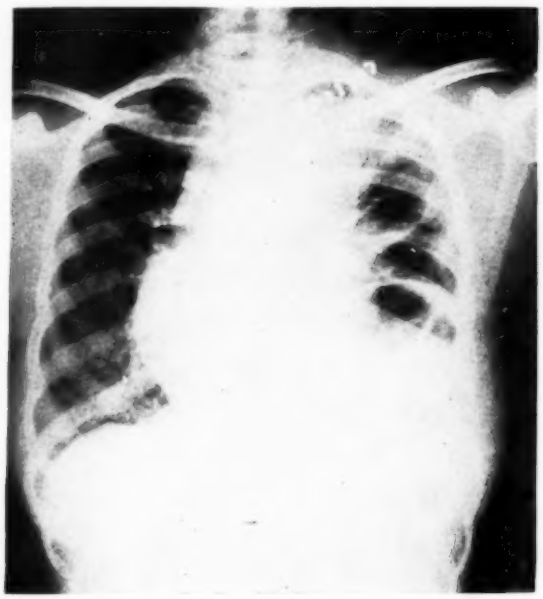

Fig. 2.—Case 1. Roentgenogram of chest on Dec. 23, 1948. Discussed in text.

On Jan. 3, 1949 (twenty-four hours before death) the patient, developing malaise and a temperature of 102.8° F. by rectum, became increasingly dyspneic within a period of five hours. The apex heart rate was 140, the rhythm remained regular, and the blood pressure was 120/80 mm. Hg. No murmurs or friction rubs were heard. The patient complained of no chest pain and had no hemoptysis. A portable roentgenogram taken at this time showed mainly atelectasis of the left upper lobe with an increase in the size and number of the patchy areas of increased density in the left lower lung field and in the entire right lung field. An electrocardiogram (Fig. 1,*C*) twelve hours before death now showed a deep S wave in Lead I with decrease in the amplitude of R in Leads I and II. There was slight S-T depression of the staircase variety in Leads I and II. Q_3 with inversion of T_3 was now present. R had become smaller in all chest leads.

T was now upright and S-T depressed in CF_5. Therapy included oxygen by mask at atmospheric pressure and intramuscular Demerol. The patient became increasingly cyanotic and dyspneic, presenting the picture of peripheral circulatory collapse without an obtainable blood pressure, and died about twenty-four hours after the onset of this terminal picture.

A necropsy (by Dr. O. Saphir) revealed a bronchogenic adenocarcinoma which had originated in the periphery of the left upper lobe and compressed the left upper lobe bronchus, producing atelectasis with infection. The tumor, invading the mediastinum, surrounded the arch of the aorta and trachea, and had extended up behind and above the left clavicle. The left pulmonary artery was completely encircled and rendered almost completely stenotic by the tumor. No pulmonary emboli were found. Metastases were evident in both lungs, peritracheal lymph nodes, ribs, skull, dura mater, brain, both kidneys, left suprarenal gland, and both ovaries (the left being involved more extensively than the right). The metastases in the lungs were nodular, and not of the type producing diffuse perivascular endolymphatic carcinomatosis. The main abnormality in the heart was moderate hypertrophy and dilatation of the right ventricle (measurements unrecorded). The liver showed chronic passive congestion. In the portion of the lung most actively invaded by tumor there were vessels showing what could be considered tumor thrombi.

Comment: It is evident in this case that pulmonary hypertension was present for some time before death since accentuation of the pulmonary second sound was heard one month before death. Congestive hepatomegaly became clinically evident three weeks before death and on necropsy definite hypertrophy of the right ventricular musculature (as well as dilatation) was found. Thompson and White have estimated that strain on the right ventricle must be present for at least two months to produce appreciable hypertrophy of that chamber.[31] During life roentgenologic examination of the heart was unsatisfactory because of the abnormalities in the left hemithorax and the elevation of the left half of the diaphragm. Although the electrocardiogram on admission to the hospital approximately one month before death showed a left axis shift (Fig. 1,*A*), this is not surprising since right ventricular hypertrophy frequently does not produce changes in the electrocardiogram until it is quite advanced. Furthermore, in this case paralysis with elevation of the left hemidiaphragm caused the heart to assume a horizontal position with some counterclockwise rotation along its longitudinal axis; hence the left axis shift.

The pathological processes producing this sustained pulmonary arterial hypertension include the following: marked constriction of the left pulmonary artery by annular infiltration of the carcinoma, marked atelectasis of most of the left upper lobe (with collapse of vessels), widespread carcinomatous metastases throughout both lungs, and the paralysis of the left hemidiaphragm which by diminished ventilation of the left lower lobe further interfered with blood flow.

That these pathological changes were progressive is evidenced by the fact that the congestive hepatomegaly appearing three weeks before death steadily became greater. The sudden downhill course terminating in death 24 hours after the onset of severe symptoms could not be explained by pulmonary embolism although the electrocardiogram was quite typical of acute cor pulmonale It is possible that gradual progression of the pathological changes described heretofore had finally. reduced the vascular bed of the lungs beyond a critical level,[32-35] undoubtedly hastened by the terminal pneumonic infection.

CASE 2.—K. R., a 21-year-old white woman, entered Winfield Hospital, Winfield, Ill., on Oct. 31, 1946, with bilateral, far-advanced, pulmonary tuberculosis. Roentgenograms revealed extensive caseous pneumonic tuberculosis of the left upper lobe with cavitation, as well as many smaller caseous pneumonic areas surrounded by large areas of exudation in the left lower lobe and scattered throughout the entire right lung (Fig. 3,*A*). The sputum was highly positive for tubercle bacilli. The patient was emaciated and ran daily temperatures up to 105° F. by rectum. Streptomycin was administered from Jan. 7, 1947 to June 6, 1947. Until March 3, 1947, she received two grams daily and then one gram daily until the streptomycin was discontinued. During this six-month period the patient demonstrated remarkable clinical improvement, gained considerable weight, and became afebrile. An accompanying improvement in the roentgenologic picture was also seen with extensive resolution of the exudative lesions in the entire right lung and in th eleft upper lobe. However, the cavity in the left upper lobe and an infiltration without discernible

cavitation in the right upper lobe remained (Fig. 3,*B*). Her sputum continued to be highly positive. Attempts to induce pneumothorax were unsuccessful. It was then felt that although the patient was a poor risk, her only chance for ultimate recovery depended upon closure of the cavity in the left upper lobe. Although roentgenologically good aeration of most of the lung appeared to be present, it was realized that very extensive destruction of the lung parenchyma had occurred, that her pulmonary reserve was definitely diminished, and that most of the pulmonary function apparently depended on the right lower lobe which at that time was least affected by the disease. Nevertheless, she was admitted to Michael Reese Hospital for a left thoracoplasty on Sept. 1, 1947.

At this time, physical examination of the chest revealed dullness in the apex of the right lung and the upper half of the left lung with exaggerated bronchovesicular breathing; a few subcrepitant râles were heard in the left apex posteriorly. Examination of the heart revealed that the second sound over the pulmonic area was louder than that at the aortic area; the rate was 90, and the rhythm was regular. No murmurs were heard. The blood pressure was 130/60 mm. Hg. Examination of the abdomen was negative. An electrocardiogram on September 2, 1947 (Fig. 4,*A*) was interpreted as being within normal limits and showing right axis shift. Fluoroscopic examination of the heart was negative. The blood count was normal; sedimentation rate was 42 mm. per hour (corrected-Wintrobe). Vital capacity was 1.5 liters as compared with a normal of 2.8 liters.

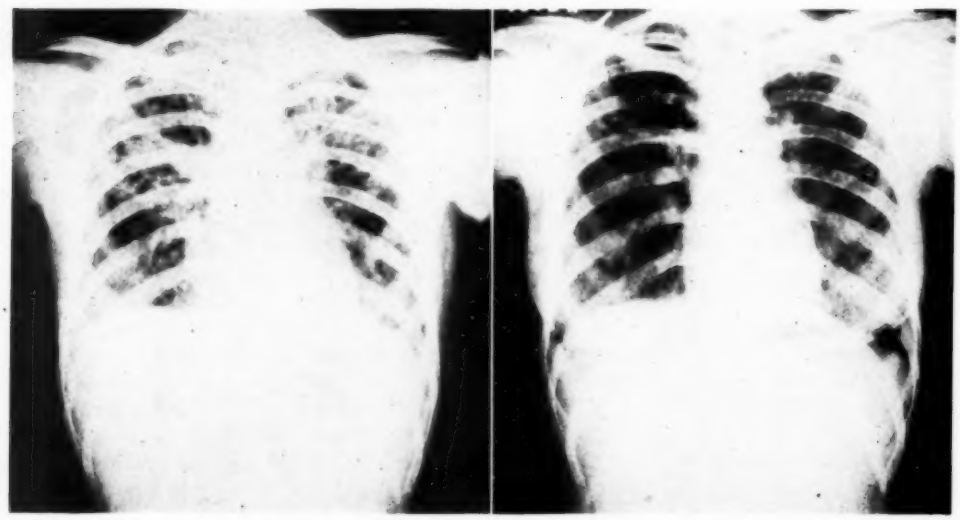

Fig. 3.—Case 2. Roentgenograms of chest. A. Dec. 27, 1946. B. Aug. 4, 1947. Discussed in text.

On Sept. 29, 1947, a first stage thoracoplasty was performed on the left side, the first, second, and third ribs being removed under cyclopropane anesthesia. Her postoperative course was uneventful. On Oct. 13, 1947, the second stage of the thoracoplasty was performed in which the fourth and part of the fifth and sixth ribs were removed. Parenteral penicillin was administered and her course was uneventful until Oct. 16 when she became mildly dyspneic and her temperature rose to 101° F. by rectum. Subcrepitant and crepitant râles were heard throughout the entire right lower chest. Her left chest was strapped to prevent paradoxical respiratory motion of the operated hemithorax. Oxygen was administered by mask at atmospheric pressure. Parenteral streptomycin was given, although it was realized that the tubercle bacilli were probably resistant to the drug at this time. She became progressively worse and 24 hours later was markedly dyspneic and cyanotic, with a pulse of 160 which was regular but of poor quality. Her respirations were 40 per minute and her temperature rose to 102° F. by rectum. She continued to become progressively worse, lapsed into stupor, and died 36 hours after the onset of her sudden decline.

An electrocardiogram taken immediately before death (Fig. 4,*B*) showed that R waves in Leads I and II were now smaller. A deeper and wider S wave and a taller P wave were now present in Lead II. S-T in Leads I and II was depressed and of the staircase variety. QRS was under 0.12 second in duration in all four leads. Auricular premature systoles were present in Leads III and CF_2. The patient stopped breathing immediately after Lead CF_2 was recorded. While oxygen was administered by mask and artificial respiration was given, further records of Leads II and CF_2 were taken (Fig. 4,*C*). These showed the agonal development of numerous nodal premature systoles (nodal escape), paroxysmal auricular fibrillation, and, in the strip of Lead II, complete right bundle branch system block.

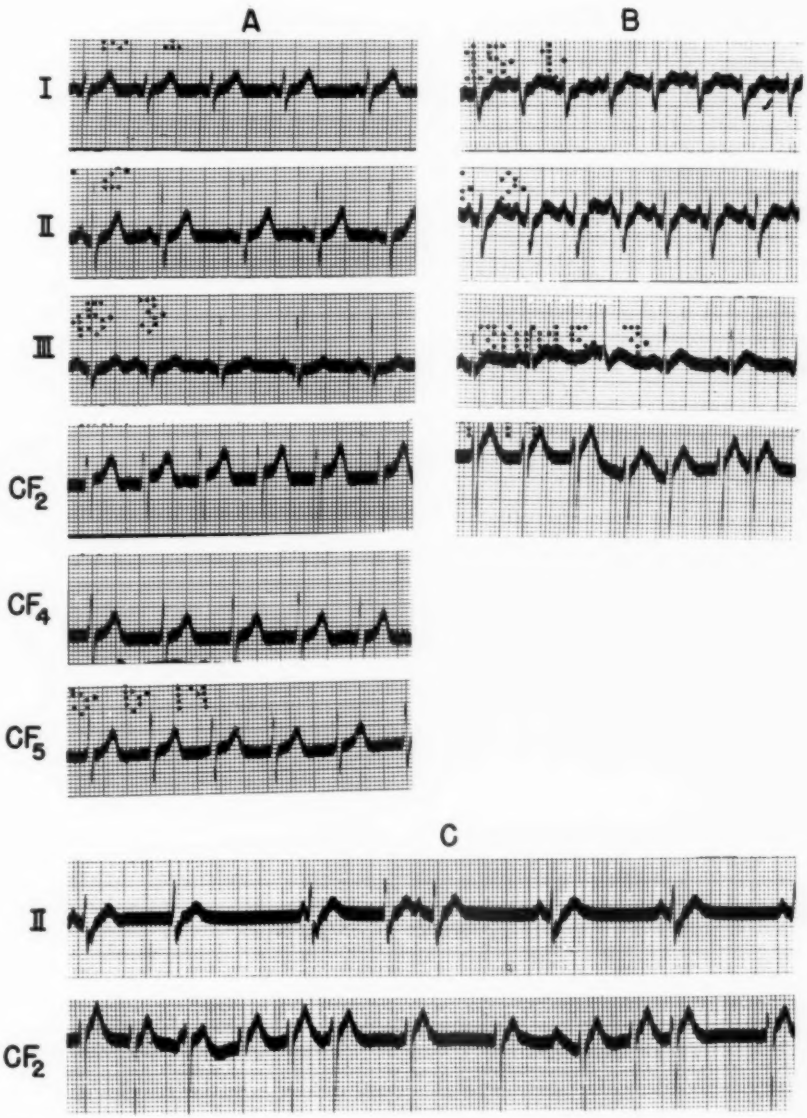

Fig. 4. Electrocardiograms of Case 2. A. Sept. 2, 1947. B. Oct. 17, 1947. C. Oct. 17, 1947 (taken during administration of artificial respiration). Discussed in text.

A necropsy (by Dr. O. Saphir) revealed that both pleural cavities were obliterated by dense fibrous adhesions. Fusiform and saccular bronchiectasis was present in both upper lobes. An acute purulent bronchitis was seen throughout both lungs. The upper half of the left lung was completely collapsed, the left upper lobe showing fibrocaseous tuberculosis with approximation of the walls of the cavities. Smaller, acinonodose tuberculous lesions with caseated centers showing signs of healing were present also in the right upper lobe. Within the upper portion of the lower lobes were tiny pinhead-sized tubercles. Many of these were encapsulated. The entire right lower lobe showed consolidation and an acute bronchopneumonia. The liver and spleen showed acute passive hyperemia. The heart weighed 240 grams. The right ventricle measured 4 mm. and the left, 16 mm. in thickness. Valves and coronary vessels were normal. There was moderate fatty infiltration of the right ventricle. Scattered throughout both ventricles, perivascularly and interstitially, were small accumulations of small and large mononuclear cells and Anitschkow cells (acute serous myocarditis). There were no pulmonary emboli.

Comment: Reconstructing the progression of pathological events that occurred before this patient's death, we may first assume that even prior to surgery this patient had pulmonary hypertension. Both indirect and direct evidence support this assumption. Indirect evidence may be assumed from the fact that before streptomycin therapy there was extensive tuberculous involvement of both her lungs. Much of this was exudative, so that after the resolution produced by the streptomycin therapy large areas were almost restored to normal. However, extensive caseation was also present destroying large areas of the lung. After partial healing these would show only deceptively minor changes roentgenographically. In addition the extensive disease undoubtedly was associated with much endobronchial disease, many focal areas of atelectasis, and other areas of air entrapment, in which blood flow was greatly reduced. It was apparent that this extensive disease destroyed a large proportion of the pulmonary vascular bed. While the capacity of the pulmonary vessels is so great that destruction or obliteration of an extremely large portion must occur before any increase in resistance in the lesser circulation is produced,[32-35] the marked accentuation of the second pulmonic heart sound is another indication that pulmonary hypertension was present at least nine months before death. Finally, hypertrophy of the right ventricle found at necropsy in the absence of coronary disease, valvular disease, or left ventricular hypertrophy justifies the assumption that pulmonary hypertension had been present for at least several months.[31]

Here, as in the first case, the absence of roentgenological and electrocardiographic evidence of right ventricular hypertrophy is not surprising.

After the second stage of the left thoracoplasty there was complete collapse at least of the left upper lobe leading to further collapse of much of the vascular bed in this portion of the lung. There was marked splinting of the entire left chest, diaphragm as well as rib cage, which usually occurs immediately postoperatively after thoracoplasty. The immobility of the remainder of the left lung thus produced led to a further increase in resistance to blood flow in the lung. The pulmonary function in this patient was therefore almost entirely dependent upon ventilation and respiratory function of the right lower lobe since much of the right upper and middle lobes were destroyed by disease.

The event that finally led to the sudden critical and fatal increase of resistance in the lesser circulation was the development of pneumonitis in the right lower lobe. This was accompanied by the obliteration of still more of the remaining vascular bed of this right lower lobe.

Furthermore, later there was added to these events a sudden weakening of the myocardium as a result of the acute serous myocarditis (found at necropsy), which has been reported as not infrequently occurring in pneumonitis. The sudden impairment of the power of the right ventricle aided the development of acute dilatation and failure of that chamber. To the major catastrophe of myocarditis also must be added the deleterious effects of fever and the marked sinus tachycardia.

The electrocardiogram seven weeks prior to death was interpreted as showing right axis shift which was compatible with a vertical heart in the narrow thin build of the patient. The electrocardiogram immediately before death showed the development of the following changes: there was marked reduction of the amplitude of the R wave as well as deepening and widening of the S wave in Leads I and II. Occasional complexes were seen in which QRS measured 0.13 second.

Diminution of amplitude of QRS in CF_2 was found. It is of importance that definite complete block of the right bundle branch system developed just before death. While it is conceivable that these electrocardiographic changes were a reflection of the myocarditis, these changes together with the clinical and necropsy findings lead inevitably to the diagnosis of acute cor pulmonale in the absence of pulmonary emboli.

The absence of the Q_3T_3 pattern with T inversion in CF_2 as described by McGinn and White[1] is not surprising since Sokolow and his co-workers[36] showed that of 50 patients with pulmonary embolism only five demonstrated these classical changes. However, in 36 instances some of the electrocardiographic changes of pulmonary embolism were present and could be termed suggestive of pulmonary embolism.

GENERAL DISCUSSION

A survey of the literature reveals other cases in which acute cor pulmonale was found in the absence of pulmonary embolism. McGinn and Spear[37] in 1941 reported the case of an 80-year-old woman suffering from a diaphragmatic hernia who died with the clinical and classic electrocardiographic picture of acute cor pulmonale. At necropsy her heart showed a chronic right ventricular hypertrophy with the acute dilatation of the right side of the heart as found in acute cor pulmonale. No pulmonary emboli were present. The etiology of the acute cor pulmonale was attributed to the sudden increase of resistance in the pulmonary circuit produced when the diaphragmatic hernia caused sudden, massive atelectasis of both lower lobes of the lung as demonstrated at necropsy. Klein[38] reported a case of acute cor pulmonale with recovery occurring in a young Negro who developed spontaneous mediastinal emphysema presumably in the absence of pulmonary embolism. All of the classic electrocardiographic changes were not present in this case.

Sporadic reports of so-called "subacute cor pulmonale"[39-41] have appeared in the literature without electrocardiographic data. The chief distinguishing feature of this condition is the rapid development of signs and symptoms of failure of the right side of the heart in patients with no history of antecedent cardiopulmonary disease or any other condition known to be capable of producing strain of the right side of the heart. It is generally produced by carcinomatous metastases from the stomach or elsewhere which cause gradual obliteration of the pulmonary vascular bed by: (1) pressure effects from the adjacent cancer-ladened lymphatic vessels, (2) connective tissue proliferation due to the desmoplastic nature of the growth, and (3) direct contact invasion of the walls of the blood vessels. Here too, pulmonary emboli are not directly involved.

It is unproductive to discuss semantically the term "subacute cor pulmonale" or to argue whether the first case presentation belongs to this group or to the group termed acute cor pulmonale. The dramatic onset of symptoms and the accelerated decline with rapid death, together with the electrocardiographic pattern of acute cor pulmonale, leads us to classify both cases as acute cor pulmonale.

More important is that the two cases illustrate that acute cor pulmonale may be produced by causes other than pulmonary emboli. In both patients the right ventricle was laboring under an increased load for, some length of time, probably several months as suggested by the right ventricular hypertrophy found at necropsy. In such patients, a sudden critical diminution in the net

diameter of the pulmonary vascular bed with resulting sudden and marked pulmonary hypertension produces a sudden increase in the burden of the right ventricle. This leads to sudden right ventricular dilatation and acute myocardial ischemia by way of the mechanisms described above. The resultant clinical and electrocardiographic picture is that of acute cor pulmonale.

If the possibility of such a terminal event is kept in mind, many patients with extensive pulmonary disease and pulmonary arterial hypertension, who decline rapidly and die after thoracic surgery (collapse or extirpative surgery), spontaneous pneumothorax, extensive pneumonitis, or any other condition which is associated with extensive collapse of the remaining pulmonary vascular bed, may under closer terminal scrutiny be seen to have died in acute cor pulmonale. This should also serve to emphasize the importance of developing a method to be used preoperatively for detecting pulmonary arterial hypertension before right ventricular enlargement is already visible roentgenologically, or before suggestive electrocardiographic findings are present, since these latter changes become noticeable clinically only after the chronic cor pulmonale is quite advanced. The catheterization of the right side of the heart and pulmonary artery for direct pressures, especially before, during and after a standard exercise may be such a method.

In addition to the inadequately emphasized causes of acute cor pulmonale described heretofore, there is a group of patients, rather infrequent in occurrence, for whom acute cor pulmonale is often the fatal catastrophe. These are the patients in whom a sudden left-to-right shunt occurs, as exemplified by rupture of an aortic aneurysm into the right side of the heart (atrium or ventricle) or pulmonary artery[42-44] and by interventricular septal rupture (due either to acute

TABLE I. CAUSES OF ACUTE COR PULMONALE

A. Marked reduction in size of the vascular bed peripherally, in the lungs.
   1. Multiple small emboli in many small pulmonary arterioles, usually repeated episodes (blood clots from venous circulation, right auricle, right ventricle; amniotic fluid emboli; direct tumor emboli; fat emboli after fractures).
   2. Endolymphatic carcinomatosis of lung.
   3. Massive destructive pulmonary disease complicated by any sudden further obliteration of the pulmonary vascular bed, as by extirpative or collapse surgery, spontaneous pneumothorax, massive atelectasis, or extensive pneumonitis (see Cases 1 and 2.)

B. Obstruction of main pulmonary artery trunk or its major branches.
   1. Massive emboli.
   2. Thrombosis.
   3. External compression by tumor (see Case 1).

C. Sudden development of left-to-right shunt.
   1. Rupture of aortic aneurysm into pulmonary artery.
   2. Rupture of aortic aneurysm into right ventricle or right auricle.
   3. Rupture of interventricular septum.
      a. Infarction of septum.
      b. Ulceration of septum with perforation in acute or subacute bacterial endocarditis.

ulcerative bacterial endocarditis or interventricular septal infarction).[45] Such patients will frequently demonstrate the clinical and electrocardiographic characteristics of acute cor pulmonale.

Table I lists the more common, as well as the more unusual, causes emphasized in this report.

SUMMARY

The functional alterations which occur in acute cor pulmonale have been considered to fall within two groups:

1. Sudden dilatation of the right ventricle with clockwise rotation of the heart along its longitudinal axis.

2. Development of myocardial ischemia, which is the result of a reduction in coronary flow, diminished oxygenation of blood flowing through the lungs, and an increased oxygen requirement of the heart as a result of its increased work.

It was shown that some of the electrocardiographic changes occurring in acute cor pulmonale may be explained by dilatation of the right ventricle and rotation of the heart; others are explained on the basis of the myocardial ischemia present.

Since the terms acute cor pulmonale and acute pulmonary embolism have frequently been used interchangeably, the purpose of this article was to demonstrate that there may be causes or precipitating factors for acute cor pulmonale, other than pulmonary embolism.

Two case reports, with necropsy, are presented in which pulmonary embolism was found absent, but in which massive destructive pulmonary disease with or without major thoracic surgery led to the development of the typical picture of acute cor pulmonale.

The term acute cor pulmonale was then extended to include also those conditions in which a sudden left-to-right shunt is produced, as occurs in interventricular septal perforation, or rupture of an aortic aneurysm into the right ventricle.

A list of the less frequent etiological conditions are presented which have been known to produce the picture of acute cor pulmonale. They all have in common a mechanism which leads to a sudden marked increase in the resistence against which the right ventricle must work.

ADDENDUM

Since the completion of this article, another patient has been seen who also exemplifies the principles emphasized above. This was a 32-year-old woman (E.S.) with extensive caseous pneumonic tuberculosis and multiple cavitation of the entire left lung, for which a left pneumonectomy was performed. A tuberculous pneumonitis developed with involvement of almost the entire right lung, leading to the rapid decline and death of the patient ten days after operation. When the extent of the tuberculous pneumonitis on the right was ascertained, it was predicted that death would be at least partially the result of acute cor pulmonale, and that electrocardiographic evidence for this event might then appear. For forty-eight hours before death, electrocardiograms were taken every twelve

hours, the last being taken two hours before death. The last two electrocardiograms showed the development of marked deepening of the S wave in Lead I, the appearance of an S wave in Lead II and a Q wave in Lead III, and slight depression of S-T in Lead I. In aV_R a tiny Q and a larger R replaced a QS deflection. In aV_L the S became deeper and the T taller. In aV_F, the R became broader and deeper (but remained quite tiny). In V_{3R} and in V_1 a less deep QS deflection replaced a tiny R which had been followed by a deep S, T became inverted, and S-T became elevated. In V_2, R became smaller, and T diphasic. In V_3, V_4, and V_5, R became smaller and S deeper than they had been formerly; the transitional zone was now present between V_5 and V_6, whereas formerly it had been between V_2 and V_3. S-T in V_5 became slightly depressed. A necropsy by Dr. O. Saphir showed extensive caseous pneumonitis of almost the entire right lung, and an interstitial myocarditis. No pulmonary embolism was found.

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THE SYNDROME OF CARDIOPULMONARY SCHISTOSOMIASIS (COR PULMONALE)

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BILHARZIC infestation of the lungs, with attending cardiac complications, occurring secondary to intestinal (*Schistosoma mansoni*) or urinary (*Schistosoma haematobium*) infestation, forms one of the several ravages of schistosomiasis in Egypt. Cases resulting from intestinal bilharziasis are invariably accompanied by bilharzic hepatic cirrhosis with or without splenomegaly.

The pathological lesion in the lungs responsible for this clinical syndrome is a widespread obliterative arteriolitis affecting the pulmonary arterioles. The bilharzia ova are wholly responsible, while the verminous infestation plays no part in producing the vascular changes. The obliterative arteritis, which usually results from repeated reinfection of the arterioles by ova, gradually leads to marked rise in the pulmonary pressure, hypertrophy of the right ventricle, and eventually right-sided heart failure. The syndrome is not uncommonly encountered in outpatients of the general hospitals in Egypt, especially in young adults of the farmer class. The clinical features may easily simulate those of rheumatic or congenital heart disease, hence the great clinical importance of this syndrome.

The first report of bilharzia ova in the lungs was made by Belleli[1] of Alexandria. Turner[2] found that in persons with urinary bilharziasis the lungs very frequently contained numerous bilharzia ova. Suarez[3] and Mainzer[4] reported clinical cases of pulmonary bilharziasis without cardiac affection. Azmy[5] in Cairo reported two instances of heart failure associated with gross dilatation of the pulmonary artery causing relative incompetence of its valve. One of the two patients died and the diagnosis was established at autopsy; the other had identical symptoms but recovered sufficiently to be discharged from the hospital. Clark and Graef[6] published the report of a patient from America whose pulmonary bilharziasis led to death from heart failure. Autopsy showed extensive arteritis in the lungs with an atheroma of the pulmonary artery but with no incompetence of its valve. Sorour[7] described in detail the pathological lesions in the lungs resulting from bilharzic infestation of this organ. He also described the parenchymatous tubercles as well as the vascular lesions caused by deposition of the bilharzia ova. Day[8] reviewed the subject of pulmonary bilharziasis and divided his patients into three main clinical groups: (1) latent, (2) pulmonary, and (3) cardiopulmonary. He described one clinical case of cardiopulmonary bilharziasis; the patient died from congestive heart failure and the diagnosis was confirmed at autopsy. This case was more or less similar to the one reported

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by Clark and Graef.[6] Shaw and Ghareeb[9] studied in detail the pathological findings in pulmonary bilharziasis. They estimated the incidence of cardiopulmonary bilharziasis, which they preferred to call "Ayerza's disease of bilharzial origin," as 2.1 per cent of all their 282 patients with schistosomiasis and 6.3 per cent of the pulmonary patients. They divide the pulmonary bilharzic lesions into:

A. Lesions due to ova.
   1. Parenchymatous tubercles only.
   2. Focal arterial lesions.
   3. Widespread arterial lesions producing Ayerza's disease.

B. Lesions due to worms.

They stressed the fact that lesions due to worms were also accompanied in 50 per cent of the cases by focal or diffuse vascular lesions due to ova and in the other 50 per cent by parenchymatous tubercles only. However, the pathological lesion which plays an important role in the development of bilharzic cor pulmonale is the widespread arterial infestation by ova. This produces an obliterative arteriolitis which is often followed by canalization of the occluding tissue. The newly formed capillaries hypertrophy producing a structure which they consider characteristic of pulmonary bilharziasis and to which they have given the name "angiomatoid." They described autopsies on six subjects with Ayerza's disease with widespread arterial lesions. None of these patients had been diagnosed clinically or before autopsy was performed. Mousa[10] and Khattab[11] described two clinical cases. Bedford, Aidaros, and Girgis[12] described a patient from Cairo who had a very advanced aneurysmal dilatation of the pulmonary artery. In their patient the diagnosis was made only at autopsy.

In spite of the early knowledge of the syndrome, cardiopulmonary bilharziasis was rarely diagnosed in the wards. Patients were often diagnosed as having idiopathic dilatation of the pulmonary artery, heart failure of unknown origin, congenital or rheumatic heart disease, or heart failure due to B_1 avitaminosis. The association of cardiac complaints with hepatosplenomegaly of bilharzic origin or with urinary bilharziasis now gives a clue to the possibility. It is the purpose of this article to discuss the syndrome from the clinical point of view and to show that even early cases of this syndrome can be diagnosed clinically.

The number of patients with cardiopulmonary bilharziasis (bilharzic cor pulmonale) admitted to Fouad I University Hospital is now, however, increasing. While in the period from 1942 to 1944 only fifteen of these patients were admitted to the hospital, the number admitted during 1945 reached thirty-four. This illustrative evidence of rise in incidence is obviously due to the greater interest recently taken in diagnosing this syndrome. The possibility is kept in mind and the condition looked for in clinics.

The syndrome is not an uncommon cause of right-sided heart failure in Egypt but it is definitely far less common than rheumatic heart disease which is prevalent among Egyptians. The ratio between the number of patients with bilharzic cor pulmonale and that of patients with rheumatic heart disease admitted to Fouad I Hospital is 1 to 23.8. It is remarkable that most of the cases diagnosed

clinically in the wards are cases secondary to intestinal bilharziasis (*Schistosoma mansoni*) and that the presence of cirrhosis of the liver with or without splenomegaly has been demonstrated in most of the cases diagnosed clinically. The syndrome also complicates urinary bilharziasis (*S. haematobium*) which is capable of affecting the lungs and producing vascular lesions. In Shaw and Ghareeb's[9] six autopsy subjects, four had bilharzic cirrhosis of the liver and in two the pulmonary infestation was secondary to pure urinary bilharziasis. These authors thought that cardiopulmonary bilharziasis occurring secondary to urinary bilharziasis would present great difficulty in diagnosis. The name "Ayerza's disease" was given to the syndrome by Shaw and Ghareeb and also by other clinicians, but it is preferable to call it "cardiopulmonary bilharziasis" as Day[8] has termed it, or, more preferably, "bilharzic cor pulmonale" for the latter explains the exact mechanism of heart failure in this syndrome. The name "Ayerza's disease" is objectionable because cyanosis is only present as a terminal event when there is advanced heart failure or if secondary pulmonary infection complicates the condition.

CASE REPORTS

Owing to the relatively small number of recorded post-mortem cases, the following case which was diagnosed clinically deserves record; it also presents some interesting myocardial changes.

CASE 1.—The patient, a farmer aged 18 years, was admitted to the hospital on Nov. 7, 1945. He complained of dyspnea on exertion, weakness, and attacks of syncope of two months' duration. He gave a history of urinary bilharziasis four years prior to admission. Examination showed clubbing of the fingers and toes, absence of cyanosis, and distention of the veins of the neck. The apex beat of the heart was heard in the fifth intercostal space 1 inch outside the midclavicular line with pulsation in the second left intercostal space. Percussion revealed impairment of note. There was also evidence of enlargement of the heart to the right. Auscultation revealed a systolic murmur present all over the heart but most marked over the mitral and pulmonary areas, with accentuation of the second pulmonary sound. The blood pressure was 130/80. A few râles were heard at the bases of the lungs. Abdominal examination showed enlargement of both liver and spleen.

Albumin was present in the urine. The stools contained ascaris ova. The hemoglobin was 85 per cent; there were 5 million erythrocytes and 13,000 leucocytes per cubic millimeter of blood. The differential count showed 12 per cent eosinophiles, 4 per cent monocytes, 36 per cent lymphocytes, and 48 per cent polymorphonuclear neutrophiles. No malarial parasites were found in the blood smears. Examination of the sputum showed no abnormality. The blood Wassermann reaction was negative. Blood circulation time was eighteen seconds (Decholin method).

X-ray examination showed enlargement of the cardiac shadow to both sides with enlargement of the pulmonary conus. The hilar shadows and lung markings were increased; there was diffuse mottling; the left lung was especially infiltrated. The picture was considered characteristic of pulmonary bilharziasis with bilharzic cor pulmonale. The aortic knob was absent; the left auricle was not found enlarged (Fig. 1).

Sigmoidoscopic examination showed multiple bilharzic papillomas but no ulcers; scraping of the rectal walls yielded *Schistosoma mansoni* ova.

An electrocardiogram revealed normal rhythm and right axis deviation (Fig. 2). The T waves in Leads II and IV were inverted; there was marked inversion of the T wave in Lead III. There was a slight RS-T depression in Leads II and III. The patient's condition gradually became worse and he died on Jan. 10, 1946, from congestive heart failure.

Post-mortem Examination.—The outer surfaces of the lungs presented small, scattered, grayish-white nodules which on palpation were quite firm. The cut surface was congested and

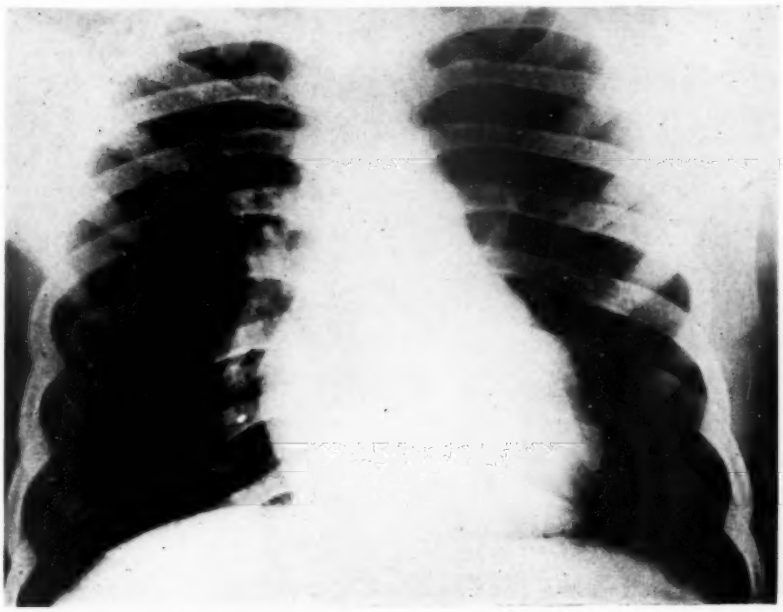

Fig. 1.—Roentgenogram of chest of Patient 1 showing pulmonary dilatation and absent aortic knob, with fine bilharzic mottling of apices. The appearance was confirmed post mortem.

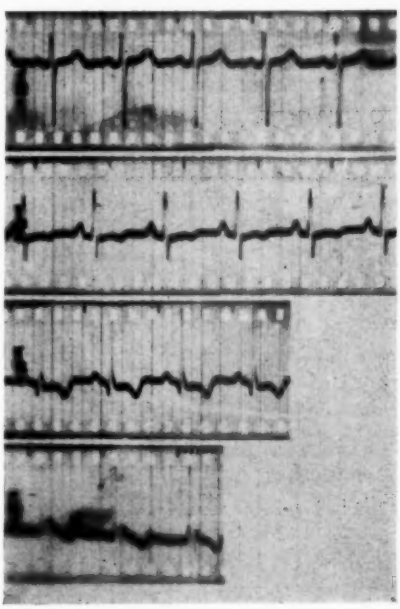

Fig. 2.—Electrocardiogram of Patient 1 showing right axis deviation and evidence of right ventricular strain.

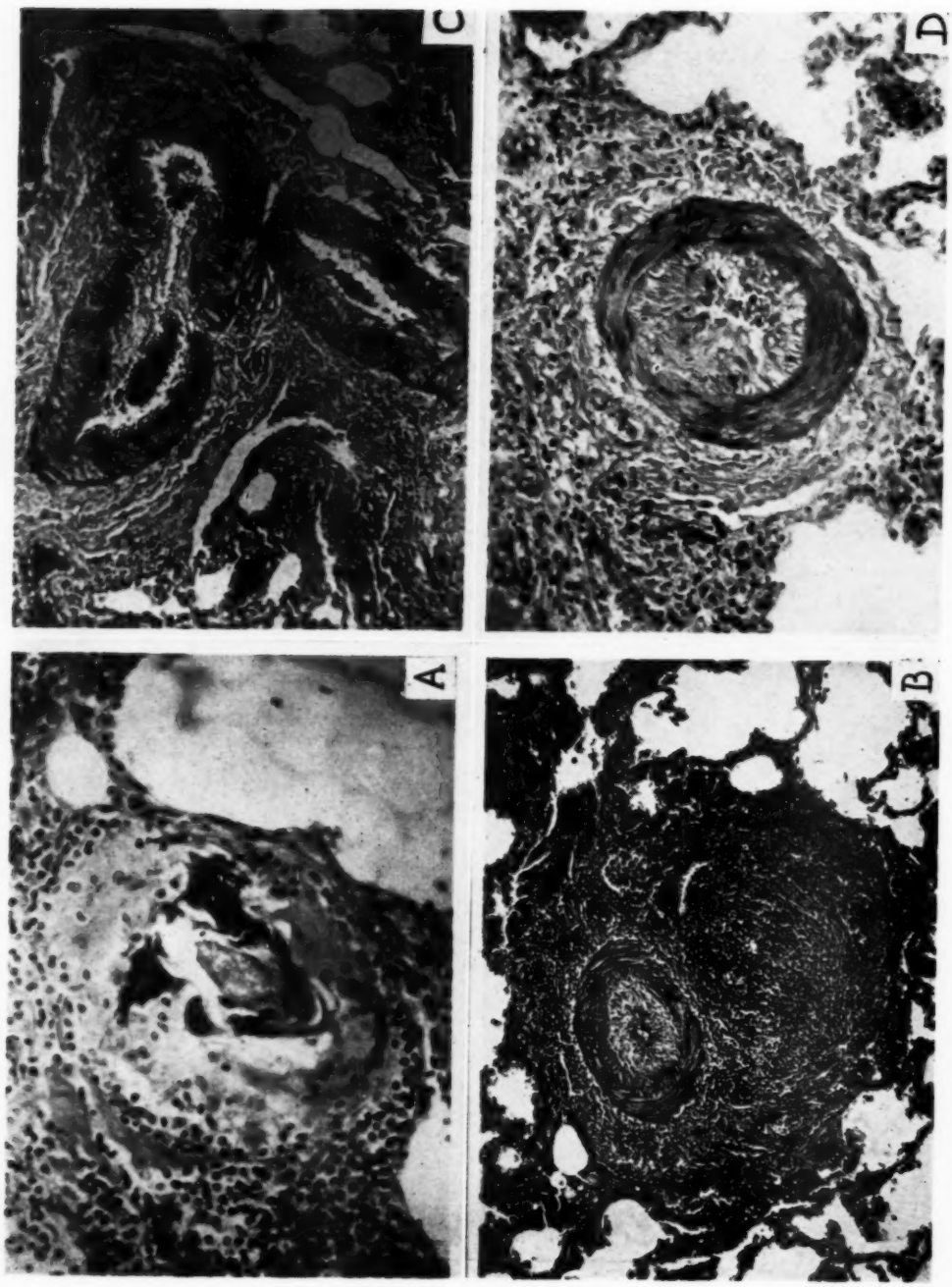

Fig. 3.—Sections from the lungs of Patient 1. *A* shows a bilharzic parenchymatous tubercle with a giant cell engulfing the chitinous shell of the bilharzia ovum. *B* shows a nearly occluded arteriole surrounded by bilharzic granulomatous tissue. *C* shows two arteries with medial hypertrophy and intimal hyperplasia consecutive to occlusive lesions in the arteriolar branches. *D* shows a small arteriole nearly occluded by canalized intimal thickening.

presented many tiny, whitish, firm nodules about 1 to 2 mm. in diameter scattered all over the surface. The main branches of the pulmonary artery showed evidence of atheroma. Some of the vessels were much thickened and apparently narrowed. The hilar lymph nodules were moderately enlarged.

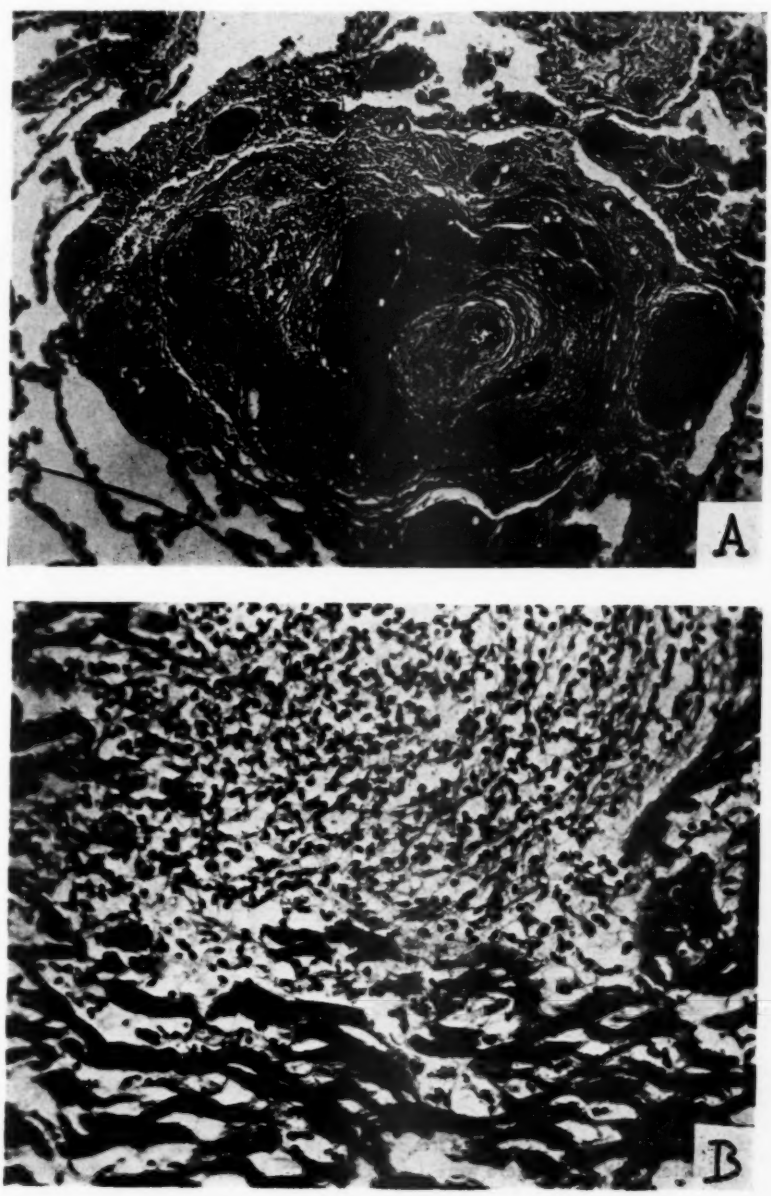

Fig. 4.—*A*, section from the lungs of Patient 1 showing the characteristic "angiomatoid" of the cavernous type forming around an occluded pulmonary arteriole.

B, section from the heart of Patient 1 showing cellular infiltration. Serial sections failed to reveal the presence of bilharzia ova.

The heart weighed 420 grams; it was definitely enlarged. The right ventricle was markedly hypertrophied; its wall was 1.3 cm. thick. The left ventricle was not distinctly thickened (1.2 cm.). The right auricle was moderately dilated and its walls rather thickened. The left auricle showed no gross changes. The main pulmonary artery was markedly dilated and showed atheromatous changes. Its circumference was 6.5 cm. while that of the aorta was 5.5. centimeters. The cusps of both arteries were healthy.

Liver showed small, flat granularity of its outer surface. The cut surface showed mild thickening of the portal tracts and congestion with mild, fatty degeneration of the parenchyma. The spleen weighed 390 grams; it was moderately enlarged. The cut surface was congested, swollen, and rather firm. Malpighian bodies were distinct. The kidneys were congested but the adrenal glands did not show any gross abnormality. The urinary bladder was contracted and showed submucous bilharzic infiltration and sandy patches. There were bilharzic papillomas in the large intestine, especially in the pelvic colon and rectum. There was also bilharzic infiltration of the mesentery of the pelvic colon.

On histologic section, the lungs showed many cellular nodules or aggregations of nodules—mostly in relation to blood vessels—which in general were composed of endotheloid cells, fibroblasts, large foreign-body giant cells, and lymphocytes. Some of the nodules contained remnants of degenerated bilharzia ova; frequently these were engulfed by the giant cell (Fig. 3, *A*). The blood vessels showed various grades of obliterative arteriolitis and some were completely obliterated (Fig. 3, *B*, *C*, and *D*). Some of the nodules were essentially formed of dense, hyaline, fibrous tissue and many of the occluded vessels were surrounded by dilated capillary or cavernous formations, the so-called "angiomatoids" (Fig. 4, *A*). The lung parenchyma also showed evidence of chronic venous congestion and patches of compensatory emphysema.

Sections from the right ventricle and auricle of the heart showed definite hypertrophy of the muscle fibers. There were a few scattered foci of cellular infiltration in the interstitial tissue of the myocardium (Fig. 4, *B*). Around the small blood vessels the cells were mostly lymphocytes together with some histiocytes, fibroblasts, and eosinophiles but there was no evidence of increased interstitial fibrosis. Such focal cellular infiltrations were also encountered within the wall of the left ventricle and auricle. Serial sections were prepared for the demonstration of bilharzia ova in the myocardium but none were found. There was fatty degeneration of the myocardium especially beneath the endocardium.

Mild bilharzic periportal fibrosis was present in the liver as well as recent cellular infiltration around sections of bilharzia worms and ova. The urinary bladder showed bilharzic submucous infiltration. In the spleen there was marked hyperplasia of lymphoid follicles and of the reticuloendothelial cells together with eosinophilic cell infiltration.

Cases 2 to 7 were clinical ones. The diagnosis was made on clinical and radiological bases. The presence of bilharzic hepatosplenomegaly in all six of these patients was suggestive of bilharzic cor pulmonale.

CASE 2.—This case is worthy of record in that the pulmonary valves became incompetent. The patient, a farmer, aged 30 years, was admitted to Fouad I Hospital on Nov. 26, 1941, complaining of dyspnea and precordial pain. On admission he showed signs of congestive heart failure, but no cyanosis was present. He was anemic and had hepatosplenomegaly, without ascites. A systolic murmur was heard over the mitral and tricuspid areas and the accentuated second pulmonary sound was followed by a soft diastolic bruit. The blood pressure was 115/70. The urine contained *S. haematobium* ova and the stools *S. mansoni*, ascaris, and ancylostoma ova.

The hemoglobin was 45 per cent; there were 4.1 million erythrocytes and 14,800 leucocytes per cubic millimeter of blood. There were 1 per cent basophiles, 12 per cent eosinophiles, 62 per cent polymorphonuclear leucocytes, 18 per cent lymphocytes, and 7 per cent monocytes. The blood Wassermann reaction was negative. The sputum did not contain bilharzia ova or eosinophiles.

X-ray examination revealed marked dilatation of the pulmonary artery as well as of the right branch, with no enlargement of the cardiac shadow (Fig. 5). The left auricle was not enlarged.

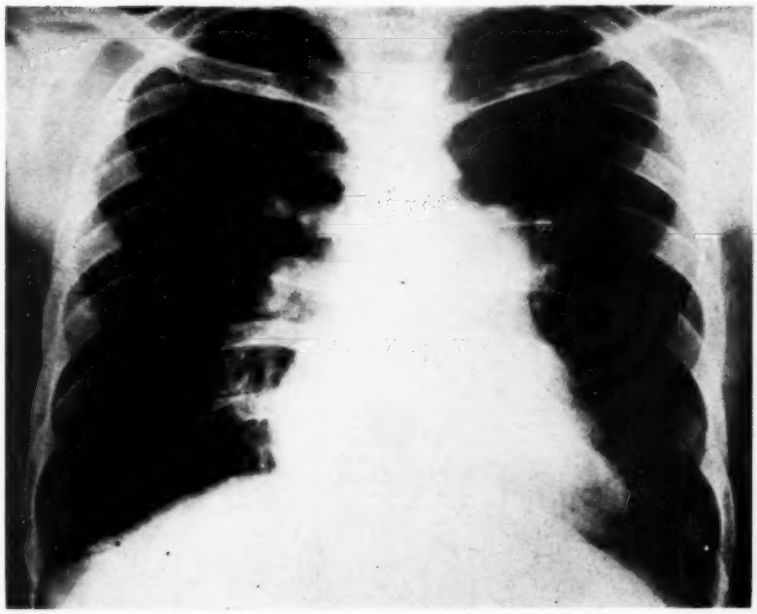

Fig. 5.—Roentgenogram of chest of Patient 2. This shows the characteristic pulmonary conus enlargement and accentuated right hilar shadow.

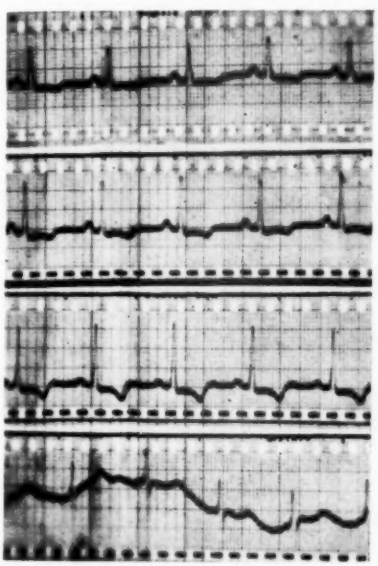

Fig. 6.—Electrocardiogram of Patient 2 shows evidence of right ventricular strain. Note the the absence of axis deviation in this patient.

Electrocardiogram showed definite depression of RS-T segments in all leads with inversion of the T waves in the standard leads (Fig. 6). Lead CF_5 did not show any abnormality.

On March 15, 1942, the patient was discharged from the hospital as improved.

CASE 3.—The patient, a farmer, aged 24 years, was admitted to the hospital on June 5, 1946, complaining of dyspnea and palpitation of four months' duration. Two years prior to admission he had bleeding from the rectum. On examination, mild clubbing of the fingers was

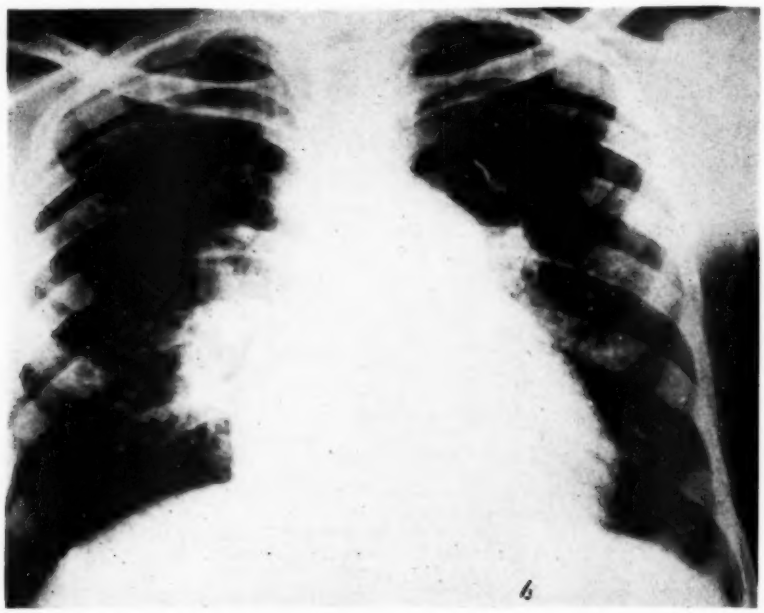

Fig. 7.—Roentgenogram of Patient 3. The pulmonary conus is enlarged and the aortic knob is absent. The right branch of the pulmonary artery is dilated. The mottling in both lungs is suggestive of bilharzic infiltration.

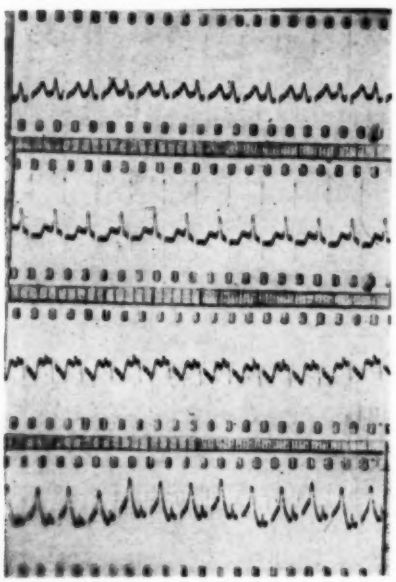

Fig. 8.—Electrocardiogram of Patient 3. Note the high P waves which are sometimes evidence of right ventricular strain.

noted, but no cyanosis was present. The pulse was regular; its rate was 94 per minute. The apex beat of the heart was 4 inches from the midline. There were pulsations in the second and third left intercostal spaces; there was a systolic murmur over the mitral and pulmonary areas but no thrill. The second pulmonary sound was markedly accentuated. The blood pressure was 100/70. The liver and spleen were enlarged. The liver showed a marked nodularity of its surface. There was no ascites. The lungs showed few rhonchi and few crepitations over both sides.

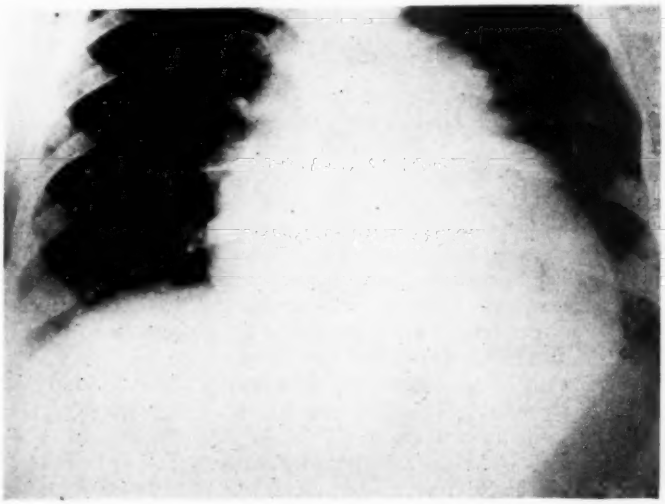

Fig. 9.—Roentgenogram of chest of Patient 4 shows gross pulmonary dilatation, absence of the aortic knob, and enlargement of the cardiac shadow.

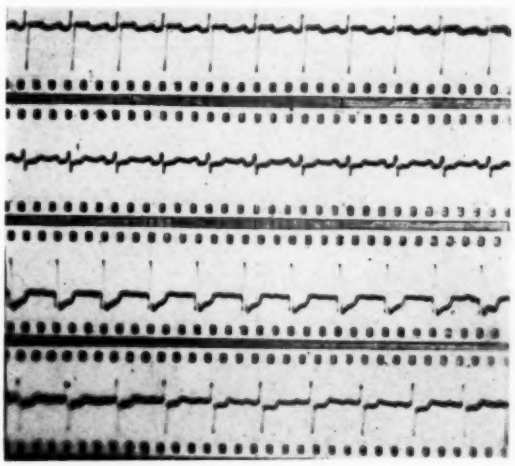

Fig. 10.—Electrocardiogram of Patient 4. (See text.)

The hemoglobin was 56 per cent; erythrocytes 3.8 million, and the leucocytes 5,600 per cubic millimeter of blood. There were 3 per cent eosinophiles, 75 per cent polymorphonuclear leucocytes, 16 per cent lymphocytes, and 6 per cent monocytes. Blood Wassermann reaction was negative. Sputum examination showed nothing peculiar. The urine contained *S. haematobium* ova and the stools *S. mansoni* ova.

X-ray films revealed a cardiac shadow enlarged to both sides with marked prominence of the pulmonary artery and its right branch and absence of aortic knob (Fig. 7). There was mottling of both lungs suggestive of bilharzic lung disease. The left auricle was not enlarged.

An electrocardiogram showed RS-T depression with biphasic T wave in Leads II and III and a tall T wave in CF_4. The P waves were prominent in Leads I and II (Fig. 8).

CASE 4.—In this case there was incompetence of the pulmonary valves. The patient was a girl 15 years of age. She was admitted to the hospital on March 26, 1946, with symptoms and signs of congestive heart failure of three months' duration. Cyanosis but no clubbing of the fingers was present. The veins of the neck were distended and there was edema of the legs. Clinically the heart was enlarged to both sides. The apex was in the sixth intercostal space 4½ inches from the midline. There was pulsation and dullness in the second and third left intercostal spaces. A systolic murmur was heard over the apex and tricuspid areas but the aortic area was normal. Over the second and third left intercostal spaces there was a systolic and diastolic murmur with accentuation of the second pulmonary sound. The diastolic murmur was accompanied by a faint diastolic thrill. The pulse rate was 90, and regular. The blood pressure was 100/70. The lungs showed crepitations over the base. The liver was enlarged and hard, but slightly tender. The spleen was enlarged. Ascites was present. Albumin was present in the urine. Examination of the stools revealed ascaris and *S. mansoni* ova. The hemoglobin was 100 per cent. There were 5 million erythrocytes and 3,600 leucocytes per cubic millimeter of blood. Four per cent of the leucocytes were eosinophiles; 70 per cent, polymorphonuclear cells; 23 per cent, lymphocytes; and 3 per cent, monocytes.

On x-ray examination the cardiac shadow appeared enlarged to both sides; there was marked dilatation of the pulmonary artery. The right ventricle was greatly enlarged. The left auricle was not enlarged. The aortic knob was absent (Fig. 9).

An electrocardiogram showed right axis deviation, a deep Q wave in Lead III, and raised RS-T segment in Lead I. The RS-T segments were depressed in Leads II, III, and CF_4. Biphasic T waves were present in the standard leads (Fig. 10).

The following case is recorded to show that the syndrome can be diagnosed clinically at an early stage.

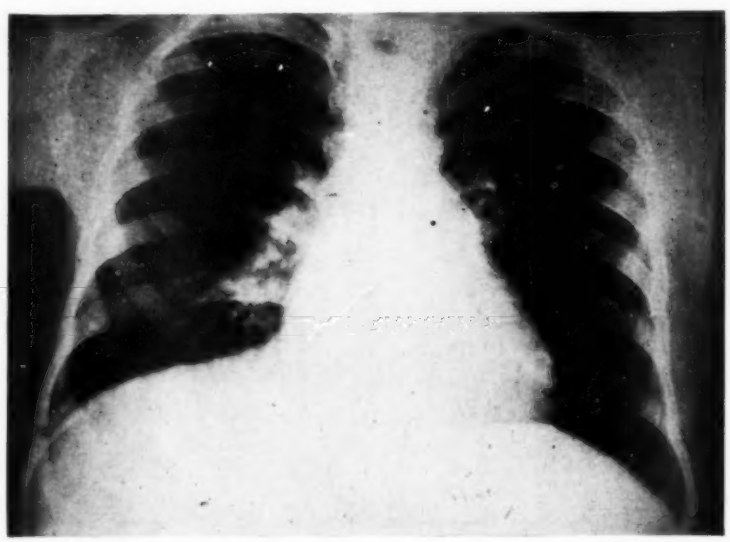

Fig. 11.—Roentgenogram of chest of Patient 5. "Mitral configuration" of the heart is demonstrated. There is evidence of bilharzic infiltration especially in the right lung; the right hilar shadow is accentuated.

CASE 5.—The patient, a boy 12 years of age, was admitted to the hospital on Jan. 9, 1946, with a diagnosis of hepatosplenomegaly and anemia. He had been complaining of dyspnea for four years. A few râles were heard over the base of the left lung. A systolic murmur was heard over the mitral and pulmonary areas of the heart, with accentuation of the second pulmonary sound. The spleen and liver were enlarged, but no ascites was present. The blood pressure was 140/80. The urine contained *S. haematobium* ova. *S. mansoni* and *S. haematobium* ova were present in the stools.

The hemoglobin was 50 per cent. There were 4 million erythrocytes and 3,600 leucocytes per cubic millimeter of blood. There were 10 per cent eosinophiles, 68 per cent polymorphonuclear cells, 19 per cent lymphocytes, and 3 per cent monocytes.

On x-ray examination the cardiac shadow was not enlarged but there was definite enlargement of the pulmonary knob sufficient to give a "mitral configuration" of the heart; the left auricle was not enlarged. There was diffuse mottling of both lungs, especially the right, and accentuation of the right hilar shadow. The whole picture was one of early bilharzic cor pulmonale with pulmonary bilharzic infiltration (Fig. 11). In this case the clinical and radiological features as well as the association with hepatosplenomegaly definitely suggested the possibility of bilharzic cor pulmonale.

An electrocardiogram showed low-voltage, raised RS-T segments in Lead II, inverted T waves in Leads I and CF_4, and biphasic T waves in Leads II and III.

The presenting symptom in the following case was hemoptysis which is a rare complaint in the syndrome and has not been noted in the foregoing cases. It was also a complaint in Case 7.

CASE 6.—The patient, a 35-year-old man, was admitted to the hospital on April 2, 1941, with a complaint of hemoptysis of two days duration. He gave a history of malaria and of passing blood in the stools ten years before admission; he had been incompletely treated with tartar emetic. On examination, the patient was found to be well nourished but anemic. He was not dyspneic and had no clubbing of the digits. His circulation rate was 16 seconds (Decholin). The blood pressure was 150/100; the pulse rate 86 and regular. Examination of the heart showed pulsations in the second left intercostal space; the apex was in its normal position. There was a harsh systolic murmur over the pulmonary area with accentuation of the second pulmonary sound.

The liver and spleen were enlarged (hepatosplenomegaly). There was no ascites. The lungs were absolutely clear. Sputum examination showed no tubercle bacilli and no bilharzia ova, but eosinophiles were present.

The hemoglobin was 96 per cent. The erythrocytes numbered 5 million, and the leucocytes, 6,000 per cubic millimeter of blood. There were 3 per cent eosinophiles, 76 per cent polymorphonuclear cells, and 2 per cent monocytes. Blood Wassermann reaction was negative. The urine contained *S. haematobium* ova and the stools *S. mansoni* ova.

On x-ray examination the heart shadow did not appear to be enlarged but there was huge dilatation of the pulmonary artery with no enlargement of the left auricle. The lungs showed enlargement of both hilar shadows but otherwise they were normal.

No electrocardiogram was made.

The following case is the only example in this small series of cases of bilharzic cor pulmonale associated with pure urinary bilharziasis. The patient's main complaints were asthmatic attacks and hemoptysis.

CASE 7.—The patient, a farmer aged 30 years, was admitted to the hospital on Dec. 7, 1939, complaining of asthma, palpitation, and shortness of breath, of four years' duration. Examination of the heart showed the apex in its normal position with pulsation in the second and third left intercostal spaces. A systolic murmur was heard over the second and third left intercostal spaces with accentuation of the second pulmonary sound. The blood pressure was

115/80. The pulse was regular. There was no clubbing of the digits. Wheezing rhonchi were heard in the lungs and there was definite prolongation of expiration.

The urine contained *S. haematobium* ova. Results of the examination of the stools were negative. The blood Wassermann reaction was negative. Sigmoidoscopic examination showed no evidence of intestinal bilharziasis. No tubercle bacilli were found in the sputum but eosinophiles were present.

The hemoglobin was 90 per cent. There were 4.6 million erythrocytes and 9,000 leucocytes per cubic millimeter of blood. There were 15 per cent eosinophiles, 60 per cent polymorphonuclear cells, 23 per cent lymphocytes, and 2 per cent monocytes.

On x-ray examination the heart showed a very marked dilatation of the pulmonary artery. In the right branch of the pulmonary artery there was a triangular shadow in the right hilar region. The left auricle was not found enlarged. The lungs showed diffuse mottling amounting to miliary infiltrations in some areas. The radiological picture was more or less similar to that of Patient 3.

An electrocardiogram showed low voltage in Lead I and ventricular extrasystoles.

During his stay in the hospital the patient had hemoptysis (about 30 c.c. of blood). A second x-ray examination revealed the same changes as were noted on the first examination. He was discharged from the hospital on Jan. 13, 1940, and died one year later from congestive heart failure.

PARASITOLOGY

Day[8] remarked that while ova were commonly found in the lungs at autopsy in patients with urinary bilharziasis (*S. haematobium*), it was remarkable that all patients with pulmonary bilharziasis reported as showing clinical symptoms had been instances of *S. mansoni* infestation. This is incorrect, as clinical cases due to *S. haematobium* have been proved (Case 7) in this series, and in the cases reported by Shaw and Ghareeb.[9]

Ova reach the lungs as emboli and are never laid by the worms in situ. In *S. haematobium* infestation the ova are readily carried to the right side of the heart and to the lungs. This explains why pulmonary infestation can occur when the urinary tract lesions are mild or early. However, *S. haematobium* produces focal and diffuse vascular lesions significantly less frequently than does *S. mansoni*. In Shaw and Ghareeb's[9] eleven patients showing pulmonary vascular pathological lesions, these latter were attributed in four instances to *S. haematobium* infestation, in six to that of *S. mansoni*, and in the remaining one the infection was mixed.

In *S. mansoni* infestation, ova are carried from the portal area through the anastomotic veins as a result of the portal obstruction caused by hepatic cirrhosis; thereafter the ova are carried to the right side of the heart and then to the lungs. At this stage the conditions are favorable for pulmonary infestation which will tend to be massive and therefore productive of arterial lesions. Such cases will be accompanied clinically by hepatosplenomegaly which finding is an aid in the diagnosis.

Coupled worms may reach the lungs also as emboli but they do not take any part in producing the vascular changes. According to Shaw and Ghareeb,[9] in 3.6 per cent of all bilharzia cases worms were found in the lungs. Both *S. mansoni* and *S. haematobium* may infest the lungs. When the worms die spontaneously or following antimony treatment they produce thrombosis in the arterioles and their toxins create an intense cellular reaction to which the name "verminous pneumonia" has been applied. Deaths due to such serious reactions have been recorded (Kenawy[13]).

PATHOLOGY

Emboli of ova reaching the lungs become impacted in the arterioles producing a specific acute necrotizing arteriolitis; the ova during their escape through the arteriolar wall destroy both the intima and media and produce extravascular parenchymatous tubercles (Fig. 3,*A*). The vascular changes are not associated with thrombosis or aneurysmal formation. When these acute vascular lesions heal, an obliterative arteriolitis develops, followed by canalization of the occluded tissue. The newly formed capillaries hypertrophy, producing a structure characteristic of pulmonary bilharziasis, called "angiomatoid." The blood spaces may grow to cavernous dimensions. When the vascular lesions are focal in distribution no effects on the heart are produced. When there is repeated reinfection, however, the vascular lesions will be sufficiently widespread to produce cardiopulmonary features. As a result of the obstruction, the proximal arteries become hypertrophied; there is associated hyperplasia of their media and thickening of their intima. After the death of the ova, the angiomatoids remain to denote the bilharzic origin of the disease. They have not been described in other forms of Ayerza's disease. In the nonbilharzic types, cavernous spaces occupy the lumen of the sclerosed arteries as they are thrombotic in origin and lie inside an intact media; this is distinctive from the nonthrombotic nature of the bilharzic angiomatoid which grows beyond the confines of the occluded vessel.

The marked rise in the pulmonary pressure is soon reflected in the main branches of the pulmonary arteries, which become greatly dilated and show atheromatous changes. The degree of dilatation is variable, and in some cases it may reach aneurysmal dimensions. In some of these advanced cases the main pulmonary arterial branches in the hila become occluded by an organized thrombus. Hypertrophy of the right ventricle develops in this disease; its wall may reach 1 cm. or more in thickness in response to the increased intrapulmonary blood pressure. The hypertrophy of the right ventricle in this syndrome is obviously in excess of that ordinarily produced by mitral disease. The gross appearance of the cut surface of the lungs in bilharzic cor pulmonale is worth studying, as this has an important bearing on the radiological appearances of the lungs which are noted in clinical cases and are now considered suggestive of pulmonary bilharziasis. In comparatively early stages, miliary nodules are seen arranged in clusters or lines round the thickened arteries. At a later stage the cut surface shows the silver-wire appearance of the thickened arteries and the absence of miliary nodules. The lungs do not show any evidence of fibrosis. The absence of pulmonary fibrosis in this syndrome distinctly separates it from other types of cor pulmonale secondary to chronic pulmonary disease.

It is surprising that Shaw and Ghareeb[9] did not attempt histologic study of the myocardium in their patients at necropsy. This may be justified by their concentration on the study of changes in the lungs and by the fact that the vascular pulmonary changes are obviously responsible for the right-sided cardiac enlargement. Clark and Graef,[6] however, found few *S. mansoni* ova surrounded by miliary foci of fibrosis in both ventricles. Strong[14] states that Africa and Santa Cruz have also found ova in the myocardium in large numbers which formed

pseudotubercles. This is reported from Japan. It was not stated whether the cardiopulmonary syndrome was associated or not. Probably this was only an accidental finding.

In Case 1 of my series there were definite cellular reactions consisting of lymphocytes, histiocytes, fibroblasts, and eosinophiles in both ventricles and auricles, but no bilharzia ova or giant cells could be demonstrated in serial sections. This cellular reaction is difficult to explain but certainly it is not rheumatic. Most probably it is related to the bilharzic infection in spite of the absence of ova. This observation should invite a further study of the myocardium in patients with bilharzic cor pulmonale.

CLINICAL PICTURE

The age incidence is usually between 12 and 35 years. Men are more frequently affected than women. The syndrome is not uncommon in Egypt, especially among persons residing in localities where bilharzia is endemic. Bilharzic cor pulmonale formed 7.5 per cent of 682 cases of Egyptian splenomegaly admitted to Fouad I Hospital during the two years prior to the time of this report. It has already been stated that the syndrome is much less common than rheumatic heart disease in Egypt. Most of the cases diagnosed clinically also manifest hepatosplenomegalic mansoniasis (Egyptian splenomegaly), but cases due to urinary bilharziasis, which are supposed to present some difficulty in diagnosis, may as well be suspected and diagnosed in the ward.

The symptoms are usually cardiac or pulmonary. Most of the patients complain of symptoms of congestive heart failure with precordial pain or syncope. Two of the patients described in this series complained of hemoptysis. This symptom has not been recorded by previous authors. Although rare, it should be recognized as an occasional symptom of bilharzic cor pulmonale. Knowledge of the pathological changes associated with the syndrome affords explanation for its occasional occurrence. Asthma was also a symptom in one of the two patients who had hemoptysis.

Cyanosis is not a constant feature of the syndrome; its absence is not due to anemia which is by no means present in every case. In fact, the limitation of the lesions to the arterioles, with healthy alveoli and capillaries, is the cause of the absence of cyanosis in some of the patients. Unless cardiac failure is well advanced or there is concomitant pulmonary sepsis, cyanosis will not be encountered.

Clubbing of the digits may be present, but is not a constant feature. It was noted in only two patients of this series. Eosinophilia has been recorded in some of the cases, but is usually absent in advanced and chronic cases. In advanced cases these are signs and symptoms of congestive heart failure, such as dyspnea, cough, engorged veins in the neck, ascites, and edema of the legs. There is tachycardia but no disturbance of rhythm. The arterial blood pressure may be low or normal. The apex beat is outside its normal position and there may be epigastric pulsation. Pulsations may be seen in the left second and third interspaces; these become dull on percussion. Over the apex a loud systolic

murmur is usually heard, and on the pulmonary area a harsh systolic murmur is audible associated with a marked accentuation of the second sound. If the pulmonary valves become incompetent, a diastolic murmur is also heard. This murmur is louder and harsher than an aortic regurgitant murmur, and may be associated with a diastolic thrill. In such cases the pulse pressure is not increased. It should be mentioned that a diastolic shock can easily be felt in many cases. The circulation rate is diminished in fairly advanced cases; that is to say the circulation time is prolonged.

Radiological Examination.—X-ray examination reveals an enlargement of the right ventricle which will form the left border of the heart instead of the left ventricle which moves counterclockwise out of view with the rotation of the whole heart; the aortic arch shares in this rotation with the result that the aortic knob appears to be absent. The heart takes the form of the familiar "mitral configuration," but there is a characteristic bulging of the pulmonary conus upwards, as a result of the gross dilatation of the pulmonary artery. The left auricle does not show any degree of enlargement. The right hilum may show a triangular shadow due to the enlarged right branch of the pulmonary artery. In advanced cases the shadow in the right hilum is dense and takes the shape of the clot (in these cases there is post-mortem evidence of an organized thrombus).

The lungs often show radiological evidence of pulmonary bilharziasis. Fine mottling of diffuse character but unlike that of tuberculous infiltrations may appear in the x-ray films in any part of the lung field. In other patients, the radiological appearance often suggests miliary tubercles which are of bilharzic nature. If tartar emetic is administered to these patients, later radiological records will show an accentuation of these shadows to the extent of a bronchopneumonic appearance. This is supposed to be an allergic phenomemon. The changes are reversible, for once tartar emetic is discontinued the shadows again regress and the field becomes much clearer.

Electrocardiographic Pattern.—In four patients of this series, electrocardiographic changes characteristic of right ventricular strain were obtained. Right axis deviation is usually present but was absent in Case 2 of the series. Inversion of the T waves, especially in Leads II and III and occasionally in Lead CF_4, was observed. Depression of the RS-T segment especially in Leads II and III was also noticed. The changes are more marked than those in the more common varieties of chronic right ventricular strain. When an organized thrombus forms in the hilar pulmonary branches, tracings similar to those noted in patients with acute cor pulmonale may be recorded. The difference will be that in the former the changes are not transient.

In Case 3 in this series prominent P waves were seen. It is well known that in chronic right ventricular strain unduly prominent P waves may be present especially in Leads II and III. In mild and early cases the electrocardiographic pattern may be more or less normal or only sometimes show a low voltage. No disturbance of conduction or rhythm was ever observed. It might be assumed that the changes in the electrocardiographic pattern in bilharzic cor pulmonale

should vary with the degree of hypertrophy and dilatation of the right ventricle which will thus form much of the anterior surface of the heart. In such an event all precordial leads would show an inverted T wave.

DIAGNOSIS

The presence of atypical cardiac symptoms and signs which may be associated with right-sided heart failure in patients who have hepatosplenomegaly or urinary bilharziasis, should arouse suspicion of the possibility of bilharzic cor pulmonale. The clinical examination should be carefully made and clinical evidence of dilatation of the pulmonary conus looked for. Radiological confirmation is always essential as the appearances are characteristic and unmistakable. Demonstration of bilharzia ova in the dejecta or in scrapings from the mucosa of the bowel may be necessary. Tests with a bilharzic antigen may be resorted to in some patients; a Wassermann test may be made to exclude the possibility of syphilitic origin of the syndrome. The sputum may be examined as a routine procedure; it may show eosinophiles, but the attempt to demonstrate bilharzia ova will be a failure.

Diseases which may simulate bilharzic cor pulmonale include: (1) rheumatic mitral incompetence, (2) patent interauricular septum, (3) patent ductus arteriosus, and (4) cardiac type of beri beri. The differentiation is easy if the possibility is kept in mind and associated visceral bilharziasis looked for. Indeed, the blowing mitral systolic murmur as well as the age of the patient may speak of a rheumatic mitral incompetence as the cause of the cardiac failure. This possibility can always be easily excluded by careful clinical and radiological examination. There is no need to say that pure mitral incompetence is a rarity. Patent interauricular septum is the only condition which closely simulates the syndrome both clinically and radiologically. In both, the pulmonary artery may be grossly enlarged and incompetence of its valves may occur. An organized thrombus may even be present in this condition (Bedford, Papp, and Parkinson[15]).

Patent ductus arteriosus can easily be differentiated by the typical machinery murmur and the lack of association with visceral bilharziasis. Marked right axis deviation should always raise the possibility of a congenital heart lesion.

In beri beri the differentiation is quite easy. In this disease edema is usually generalized and there is a general cardiac dilatation involving the conus. The therapeutic response to vitamin B_1 is dramatic.

As in Case 5 of the series, there is no doubt that routine clinical examination of the heart in suspected cases, supplemented by a radiological examination, must enable one to detect even early cases showing a "mitral configuration" in the x-ray film.

It remains to be said that genuine rheumatic heart disease, such as mitral stenosis, may be actually associated with hepatosplenomegaly. In one of these patients, who had mitral stenosis and auricular fibrillation, the pulmonary conus was so much enlarged that the possibility of the combination of mitral stenosis with bilharzic cor pulmonale was raised more than once. Only post-mortem examination could settle the question. The degree of pulmonary enlargement was more than could be accounted for by a pure mitral stenosis. This possi-

bility could be analogous to the association of mitral stenosis with patent interauricular septum, i.e., Lutembacher's syndrome. I should like to draw attention to the possibility of such a combination in some instances.

TREATMENT

The presence of heart failure is an absolute contraindication to the use of antimony; digitalis and mercurial diuretics are to be administered. In order to diminish the number of persons victimized by this serious syndrome, patients with hepatosplenomegaly and urinary bilharziasis should receive the specific treatment at an early stage. A full course of antimony should be given. In the opinion of Day,[8] *S. mansoni* is more resistent to treatment than *S. haematobium*, therefore a longer course should be given to eradicate the former. I should like to issue a warning against the use of the so-called intensive antimony treatment. The drug is a myocardial poison.

SUMMARY

Seven cases of bilharzic cor pulmonale were described. In one of the patients necropsy was performed and the detailed pathological findings recorded. In the myocardium of this patient, scattered foci of cellular infiltrations consisting mainly of lymphocytes, some histiocytes, fibroblasts, and eosinophile cells were demonstrated. No bilharzia ova were seen. The clinical, radiological, and electrocardiographic findings were fully described. Stress was laid on the possible diagnosis of concomitant pulmonary bilharzic infiltrations and their radiological appearances. Diagnosis of early cases can be made and confirmed radiologically. The x-ray appearance is that of the well-known "mitral configuration."

The responsible lesions are mainly vascular, consisting of obliterative arteriolitis, produced by the passage of bilharzia ova through the arteriolar wall in an attempt to form extravascular parenchymatous tubercles. Healing of the intimal and medial lesions results in obstruction, which in some arterioles is complete. This is eventually followed by dilatation and atheroma of the main pulmonary artery and by marked hypertrophy of the right ventricle. In advanced cases the occluded tissue becomes canalized and expanded by capillary or cavernous formations to form the "angiomatoid" which is a characteristic feature of bilharzic arteriolitis.

The symptomatology was discussed. Hemoptysis was observed in two patients in the series. It was stressed that the term "Ayerza's disease" was unfortunately applied. A better terminology is "cardiopulmonary bilharziasis" or, still better, "bilharzic cor pulmonale."

Cyanosis is not a constant feature of the syndrome and is only present when heart failure sets in, or if there is concomitant pulmonary infection with septic organisms (such as chronic bronchitis). Clubbing of the digits is also not constant, but may be present in a good number of patients.

The author is greatly indebted to Professor Arafa for permission to record Case 4, and to Dr. Hashem, Assistant Professor of Pathology, for the pathological report and the detailed histological study of Case 1. He also wishes to thank Bakr Effendi Seoudi for the microphotographs, and Mamdouh Effendi for the x-ray photographs.

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THE EFFECT OF DICUMAROL UPON THE MORTALITY AND INCIDENCE OF THROMBOEMBOLIC COMPLICATIONS IN CONGESTIVE HEART FAILURE

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RECOGNITION of the frequency and seriousness of thromboembolic complications in congestive heart failure led us to study a series of cases in which Dicumarol was given to half the patients and withheld from the rest. Early results, in a series comprised of 61 patients treated with Dicumarol and 58 control subjects, were encouraging but far from conclusive.[1] Wishart and Chapman,[2] in a similar study, also reported encouraging but inconclusive results. The present report includes the subjects of our earlier series and an additional number which brings the total up to 335.

METHOD

Prothrombin activity of the blood plasma was determined upon admission in all patients with congestive heart failure by the Brambel modification[3] of Quick's method. Patients in whom prothrombin activity was normal or near normal fell into the treated and control groups; those in whom prothrombin activity was initially below 50 per cent of normal constituted a third, low prothrombin group in which Dicumarol was not used.

In the earlier series alternate patients admitted to each medical ward of the Louisiana State University service were allotted to the treated and control groups; in the later series the treated and control groups were alternated weekly between the Tulane and Louisiana State University units and rotated at the same intervals among the wards of the Independent unit.* There were thus patient alternation, service alternation, and ward rotation in allotting the patients to the two groups.

Dicumarol administration was begun within 24 hours of admission in the usually accepted dosage with usual precautions, the aim being to maintain plasma prothrombin activity between 10 and 30 per cent of normal throughout the hospital stay. We controlled only the administration of the anticoagulant; all other therapy was prescribed by the visiting and resident staffs of the respective wards.

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*Grateful acknowledgment is made to Dr. George Burch, Head of the Department of Medicine, Tulane University, and to Dr. J. O. Weilbaecher, Jr., Head of the Medical Service, Independent Unit, for their kindness in permitting us to include their patients in the study.

CHARACTERISTICS OF THE SERIES

In 38 patients, about an eighth of the total, initial prothrombin activity was less than 50 per cent of normal. This low prothrombin group, too small as yet for valid comparison with the treated and control groups, is excluded from consideration in the present report.

Of the 297 patients whose plasma prothrombin was normal or near normal, 147 fell by lot into the treated group, 150 served as control subjects. The two groups proved to be closely similar in the distribution of cases according to etiology (with the exception of a comparative predominance of congenital heart disease in the treated group), age, sex, race, and severity of failure (Tables I, II, III, IV). The incidence of auricular fibrillation was almost the same in the two groups—25 per cent in the treated patients, 22 per cent in the control subjects.

TABLE I. ETIOLOGY

DIAGNOSIS	TREATED PATIENTS		CONTROL SUBJECTS	
	NUMBER	INCIDENCE (PER CENT)	NUMBER	INCIDENCE (PER CENT)
Hypertensive-arteriosclerotic	116	78.9	120	80.0
Rheumatic	8	5.4	7	4.7
Syphilitic	15	10.2	18	12.0
Congenital	7	4.8	1	0.7
Hyperthyroidism	1	0.7	2	1.2
Beriberi	0	0	1	0.7
Cor Pulmonale	0	0	1	0.7
Totals	147	100	150	100

TABLE II. AGE

RANGE	TREATED PATIENTS		CONTROL SUBJECTS	
	NUMBER	INCIDENCE (PER CENT)	NUMBER	INCIDENCE (PER CENT)
20 to 29	3	2.0	1	0.7
30 to 39	4	2.7	9	6.0
40 to 49	27	18.4	33	22.0
50 to 59	33	22.4	37	24.7
60 to 69	43	29.2	36	24.0
70 to 79	35	23.8	32	21.3
80 to 89	2	1.4	2	1.3
Totals	147	100	150	100

It was not possible to obtain trustworthy data regarding the number of bouts of failure sustained by many of the patients or the date of onset of the initial symptoms, but in an attempt to get at least minimal information regarding the

time factor, the groups were broken down according to the time elapsed since the first admission to Charity Hospital for congestive heart failure. Again, the groups appear similar: in the treated group, 32 per cent of the patients had first been admitted a year or more before they fell into our series, and in 68 per cent the first admission dated back less than a year; corresponding figures for the control group were 29 per cent and 71 per cent.

TABLE III. RACE AND SEX

	TREATED PATIENTS		CONTROL SUBJECTS	
	NUMBER	INCIDENCE (PER CENT)	NUMBER	INCIDENCE (PER CENT)
White men	40	27.2	32	21.3
Negro men	42	28.6	54	36.0
White women	22	15.0	19	12.7
Negro women	43	29.2	45	30.0
Totals	147	100	150	100

TABLE IV. SEVERITY OF FAILURE

	TREATED PATIENTS		CONTROL SUBJECTS	
	NUMBER	INCIDENCE (PER CENT)	NUMBER	INCIDENCE (PER CENT)
Mild	31	21.1	39	26.0
Moderate	53	36.0	50	33.3
Severe	63	42.8	61	40.7
Totals	147	100	150	100

RESULTS

Effects of Dicumarol.—Adequate reduction of plasma prothrombin activity (10 to 30 per cent of normal) was attained in approximately 90 per cent of the 147 patients treated with Dicumarol, usually within 48 to 72 hours.

Menadione was given to 12 patients in whom prothrombin activity had fallen below 10 per cent of normal. Microscopic hematuria was noted in several patients, and in one there was gross but not serious bleeding from the bladder. Transfusions were not given to any of the patients.

Mortality.—There were 11 deaths in the treated group, a mortality of 7.5 per cent. In the control group there were 20 deaths, a mortality of 13.3 per cent (Table V).

TABLE V. MORTALITY

	TREATED PATIENTS	CONTROL SUBJECTS
First Series[1]		
Number of patients	61	58
Number of deaths	7	10
Mortality (per cent)	11.5	17.2
Second Series		
Number of patients	86	92
Number of deaths	4	10
Mortality (per cent)	4.6	10.9
Combined Series		
Number of patients	147	150
Number of deaths	11	20
Mortality (per cent)	7.5	13.3

Fatal thromboembolism.—Autopsy was obtained in only three patients in the treated group; in none of these were thrombi, emboli, or infarctions found. There were eight deaths in which autopsy was not permitted. In none of these patients were there definite clinical signs of thromboembolic complications, although one patient died rather suddenly in a shock-like state on the eighth hospital day.

Autopsy was obtained in 10 of the 20 patients who died in the control group; in eight of these evidence of thrombosis or embolism was found, and in seven recent infarction of the brain, bowel, lungs, or myocardium appeared to have played a major role in the death of the patients (Table VI). Of the 10 patients in whom autopsy was not permitted, two had presented definite clinical signs of severe pulmonary embolism shortly before death, and in four others death was rather sudden and unexpected.

Nonfatal thromboembolism.—One patient who fell into the treated group had evidently sustained a pulmonary embolism of moderate severity shortly before admission; in two others of this group definite clinical signs of acute pulmonary infarction appeared during the first 48 hours after admission, in each instance before plasma prothrombin activity had been reduced to a "therapeutic level." These three patients recovered.

In two of the control group clinically recognizable nonfatal acute pulmonary infarction occurred; Dicumarol was used in the treatment of one of these patients who nevertheless remains in the control group.

Total incidence and mortality of thromboembolism.—The incidence of definite or proved thromboembolic complications is quite low in this series—2 per cent in the treated patients, eight per cent in the control subjects (Table VII). No fatalities are definitely ascribable to thromboembolism in the treated group, but it is reasonably certain that thromboembolic complications were major or principal factors in the death of nine subjects of the control group—almost half of the deaths in this group.

TABLE VI. AUTOPSY EVIDENCE OF THROMBOEMBOLISM

CASE NUMBER	GROUP	CLINICAL CHARACTERISTICS	AUTOPSY FINDINGS
1	Control	Negro woman, aged 63 years Syphilitic heart disease	Bilateral auricular thrombi Gangrene of jejunum
2	Control	White woman, aged 51 years Hyperthyroid heart	Mural thrombus left ventricle Small pulmonary infarct
11	Control	White man, aged 43 years Hypertensive heart disease	Multiple pulmonary infarctions
12	Control	Negro man, aged 49 years Hypertensive heart disease, atrial fibrillation	Massive pulmonary infarctions
14	Control	Negro woman, aged 54 years Syphilitic heart disease	Pelvic thrombophlebitis Multiple pulmonary infarcts
15	Control	Negro man, aged 55 years Hypertensive arteriosclerotic heart disease, atrial fibrillation, sudden death fifth hospital day.	Multiple infarcts of myocardium
17	Control	Negro man, aged 66 years Arteriosclerotic heart disease, melena twenty-fourth hospital day, death two days later.	Mesenteric thrombosis, infarction of bowel, peritonitis
18	Control	White woman, aged 70 years Arteriosclerotic heart disease.	Multiple pulmonary infarctions

TABLE VII. DEFINITE OR PROVED THROMBOEMBOLISM—INCIDENCE AND MORTALITY

	TREATED PATIENTS	CONTROL SUBJECTS
Total number	3	12
Incidence (per cent)	2	8
Number of deaths	0	9

DISCUSSION

If the clinical characteristics of the treated and control groups are actually as nearly identical as they seem to be, the difference in mortality rates of the two groups is statistically significant and attributable to the effect of Dicumarol therapy upon the incidence of major thrombotic complications. The probability of significance is increased by the following considerations:

(1) In view of the well established facts that thromboembolic complications play an important role in the mortality of congestive heart failure and that Dicumarol is effective in the prevention of intravascular thrombosis and embolism, it is reasonable to expect a lowering of mortality from the carefully controlled use of this drug.

(2) The difference in mortality appeared early in the study, and was consistently maintained as the number of patients increased.

(3) The data indicate that the incidence of major thromboembolic complications was very low in the treated group, but that at least nine deaths among the control subjects were due largely or principally to such complications. If these nine deaths are excluded from the control group, the mortality is reduced to 7.8 per cent—almost exactly that of the treated cases.

SUMMARY AND CONCLUSION

Dicumarol was used as an adjunct to the therapy of 147 patients with congestive heart failure, and a contemporary group of 150 subjects were used as controls. The mortality was lower and the incidence of thromboembolic complications less in the group of patients who received Dicumarol. The data suggest that the carefully controlled use of anticoagulants may improve considerably the chances of recovery from individual bouts of congestive failure.

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THE EFFECTS OF MAGNESIUM UPON CARDIAC ARRHYTHMIAS

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IT HAS long been known that the magnesium ion has a distinct influence upon cardiac activity. Clinical application of this action was reported in 1935 by Zwillinger[1] who showed striking, though temporary, success in abolishing extrasystoles caused by digitalis. However, magnesium has not been employed widely for this purpose and available reports on the subject are few.

This study was undertaken in order to re-examine the influence of magnesium upon various arrhythmias, chiefly those associated with digitalis administration and including definite digitalis intoxication. Altogether 25 patients were studied, of whom only one had no demonstrable heart disease. The others had arteriosclerotic, hypertensive, or rheumatic heart disease, and were in mild to moderate degrees of decompensation. Their rhythmic mechanisms were as follows: ventricular extrasystoles, 14 (sinus rhythm, 6; auricular fibrillation, 8; with digitalis intoxication, 10; no digitalis given, 4); incomplete heart block (prolonged auriculoventricular conduction from digitalis intoxication), 1; complete heart block (no digitalis), 1; sinus arrest (digitalis intoxication), 2; auricular flutter without extrasystoles (digitalis but no toxicity), 2; and auricular fibrillation without extrasystoles (digitalis but no toxicity), 5.

METHOD

Magnesium sulfate was given intravenously in 20 per cent solution. All patients received 20 c.c. of the salt, the injection being made as rapidly as possible. The injection usually was completed in 4 to 10 seconds, the beginning and end being indicated on the electrocardiogram. Continuous electrocardiographic recording was made for the first minute or two after the start of injection, and further records at short intervals thereafter whenever visual observation of the string shadow indicated a change in rate or rhythm. When ventricular extrasystoles were present their frequency was expressed as a fraction indicating the number of extrasystoles among the total number of ventricular beats counted. Since short strips often show variation in the frequency of extrasystoles every effort was made to count at least 100 consecutive beats in order to obtain a truer value of their occurrence.

RESULTS

Twenty-nine injections of magnesium sulfate were given to 25 patients. In each case there was a subjective sensation of heat in the upper parts of the body

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TABLE I. EFFECTS OF MAGNESIUM SULFATE

CASE	AURICULAR RHYTHM*	FREQUENCY OF VENTRICULAR EXTRASYSTOLES	30 TO 60 SECONDS	1 TO 2 MINUTES	2 TO 3 MINUTES.
5	AF	46/100		6/100	12/100
7	AF	40/100		14/100	44/100
10	RSR	12/100	0/80	0/100	0/60
11	AF	30/100†	12/100	0/70	40/80
13	AF	33/100			0/60
13	AF	12/100		2/100	0/100
14	RSR	25/100	1/16	0/50	1/150
16	RSR	6/70		5/100	0/50
22	AF	43/100		0/106	25/100
24	RSR	58/100		0/100	0/100
24	RSR	50/100			0/100
25	AF	25/100	11/50	20/50	6/100
29	AF	16/100	20/50	20/100	3/100
31	RSR	14/100	3/100	0/40	0/75
44	RSR	50/100		0/250	1/25
45	AF	26/100	28/100		34/100

*AF, auricular fibrillation; RSR, regular sinus rhythm.

†An additional 28 beats out of the 100 were aberrant in form but not extrasystoles.

Numbers in columns 4, 5, 6 and 7 are aligned according to whether they refer to observations made at beginning, middle or end of observation periods stated in column heading.

and in most cases there was visible reddening of the blush areas. These changes appeared within a few seconds of the end of the injection, and were occasionally quite unpleasant to the patients. However, there was little apprehension, since all patients had been forewarned and expected the reaction. On one occasion, (Case 7, Table I) after about 6 c.c. had been injected there was accidental extravenous infiltration of about 5 c.c. The infiltration proved to be innocuous both subjectively and objectively. Sometimes during the course of injection, but usually a few seconds after it, the electrocardiogram showed numerous continuous

UPON VENTRICULAR EXTRASYSTOLES

4 TO 6 MINUTES	LATER	REMARKS	DIGITALIS
32/100			Digitalis leaf intoxication
32/100		6 c.c. magnesium given.	Digitoxin intoxication
0/100	14 minutes : 14/100		None
30/100		Marked slowing of ventricular rate in 2 minutes including 1 pause of 2.2 seconds.	Digoxin intoxication
0/170			Digitoxin intoxication
0/100	8 minutes : 8/100	Magnesium repeated 3 hours after above.	Digitoxin intoxication
0/200	8 to 20 minutes	Ventricular extrasystoles returned in 30 minutes.	None
5/100		Ventricular rate fell from 63 to 42 in 2½ minutes.	Digitalis leaf intoxication
10/230	30 minutes : 30/80	Bidirectional extrasystoles appeared at 3 minutes.	Digilanid intoxication
20/100	30 minutes : 50/100		None
50/100	Bidirectional ventricular tachycardia lasting 6 seconds appeared in 9 minutes. Bigeminy returned in 10 minutes		Digitalis leaf intoxication
8/100	Bidirectional trigeminal groups for a few seconds in 1½ minutes		Digitalis leaf intoxication
1/200	20 minutes : 30/100		Digoxin intoxication
2/150	30 minutes : 15/100		Digoxin intoxication
9/30	20 minutes : 35/100	Ventricular rate increased from 72 to 125 in 2 minutes.	None
50/100		Ventricular rate fell from 102 to 66 in 5 minutes	Digitalis leaf intoxication

artifacts. These rarely lasted for more than 30 seconds, and were often too minor to mar the record. They appeared usually as sharp, frequent oscillations in the base line and T wave.

1. *Ventricular Extrasystoles.*—Sixteen trials were made in 14 cases. Table I shows the striking diminution or abolition of extrasystoles in every instance but one (Case 45). It will be noted that this occurred within four minutes, and often in less than one or two minutes after the end of injection. A characteristic response is shown in Fig. 1. Almost always the effect wore off in a few minutes, and lasted as long as 30 minutes in only one case. Often either before or after the reduction in extrasystoles, magnesium caused a transient increase in their frequency, and occasionally extrasystoles from new foci appeared for a few

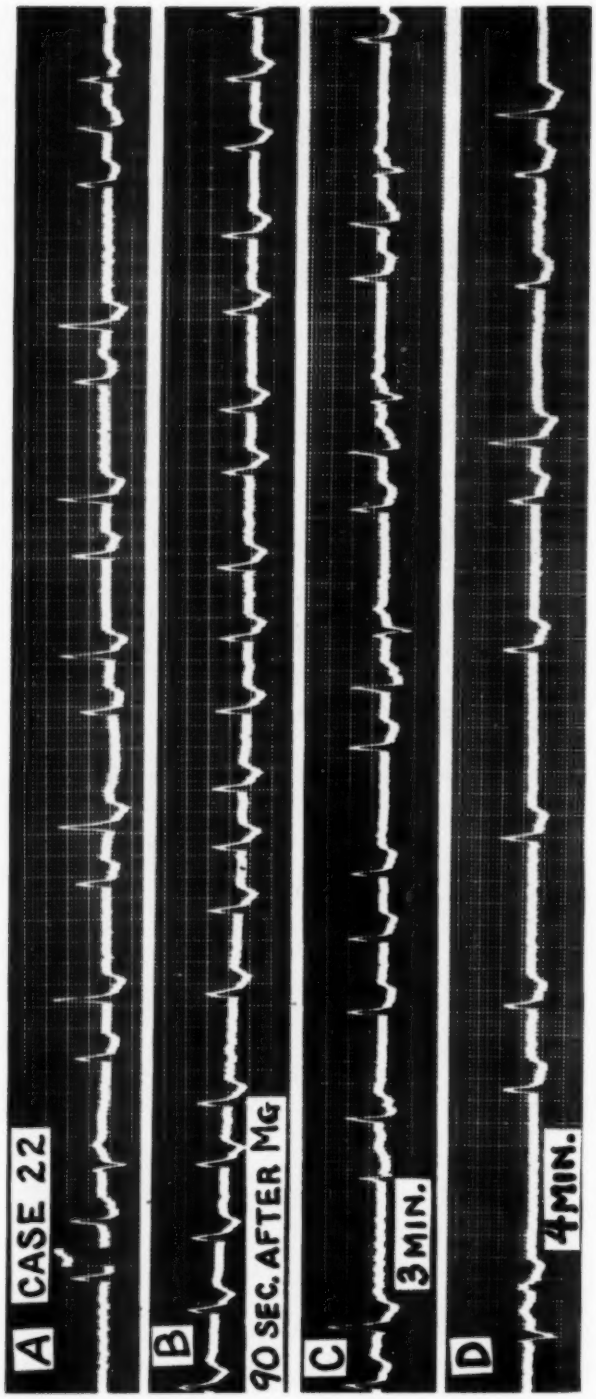


Fig. 1.—The effects of magnesium upon ventricular extrasystoles.

seconds. On one occasion (Case 24) a bout of bidirectional ventricular tachycardia lasting six seconds appeared just before the magnesium effect was dissipated. Extrasystoles were not provoked in any patient in this series in whom they had been absent prior to administration of magnesium.

2. *Incomplete Heart Block.*—In one patient, (Case 28) the P-R interval was shortened from 0.29 to 0.27 second as the rate increased from 90 to 120 in one minute (Fig. 2). There was no further change for five minutes, when Wenckebach periods appeared with P-R intervals up to 0.39 second. In six minutes the effect was gone.

3. *Complete Heart Block.*—In one patient with a ventricular rate of 20, the only change found was a transient sinus tachycardia with unaltered ventricular rate. The effects wore off within eight minutes.

4. *Sinus Arrest.*—Two patients exhibiting this arrhythmia showed similar responses. Case 20 (Fig. 3) received magnesium sulfate on three occasions, a week apart, while her digitalis was being continued. Each time the mechanism of sinus arrest was abolished within 30 seconds, and replaced by sinus tachycardia. The effects endured for 20 minutes, 4 minutes, and 3 minutes. There was sudden inversion of the T wave and shortening of the P-R interval during the tachycardia.

Case 17 had sinus arrests every three to ten beats, followed by sinus and auriculoventricular nodal escapes. In one-half minute after magnesium sulfate, the sinus arrests disappeared and the heart rate increased slightly. In three minutes the sinus arrests reappeared and the P-R interval increased to 0.28 second. For the next two minutes the arrests were more frequent and the escapes from arrest were all by the auriculoventricular node. In 15 minutes the effect was completely dissipated.

5. *Auricular Flutter.*—In two patients with auricular flutter, both on digitalis, the magnesium effects were contradictory. The ventricular rate increased in one and fell in the other. In the latter patient the fall in rate was due to transient increase of auriculoventricular block from 2:1 to 4:1.

6. *Auricular Fibrillation.*—Of five patients on digitalis without premature beats, sharp effects occurred in two. These showed slowing of the ventricular rate, from 88 to 50 in one patient, and from 66 to 20 (!) in the other. The action appeared in each instance within one-half minute and wore off in four and two minutes, respectively.

7. *Auriculoventricular Conduction.*—In normal sinus rhythm, with or without premature beats, alterations of the P-R segment were neither striking nor uniform. Within the first minute or two there was usually slight shortening of the P-R interval, and after two minutes there was, occasionally, some lengthening. The largest change was in Case 31 where the P-R interval increased from 0.16 to 0.20 second in two minutes. The initial shortening and later lengthening of the P-R interval in incomplete heart block and sinus arrest have already been mentioned.

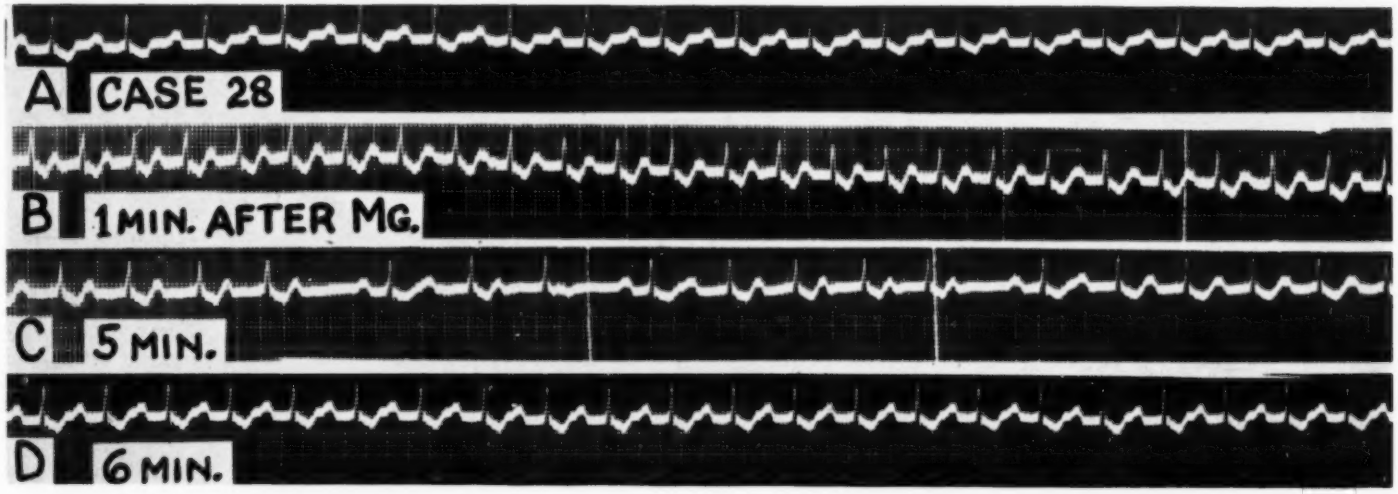
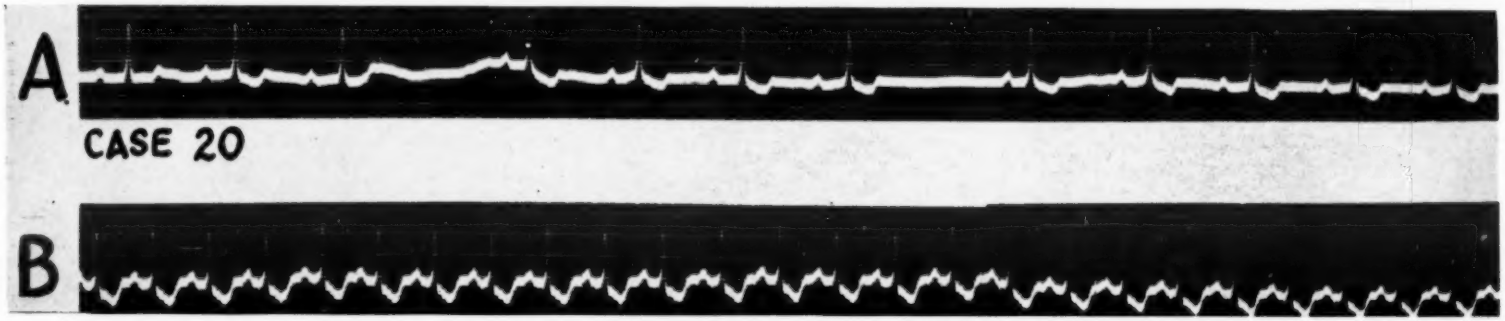


Fig. 2.—Lead II. The effects of magnesium on a patient with incomplete heart block (prolonged auriculoventricular conduction).



(30 seconds after magnesium)

Fig. 3.—Lead II. Effects on a patient with frequent sinus arrests. The timer was not in motion during the recording, but the paper transport speed was normal.

8. *T Wave.*—This deflection was usually made more negative in Leads I or II by magnesium, though the magnitude of this change was rarely great. This, like other magnesium effects, was of short duration.

9. *Rate.*—Almost always, regardless of the rhythm, the initial result was a slight to moderate increase in auricular rate when a sinus mechanism was present, and in ventricular rate during auricular fibrillation. Usually before the effect was dissipated the rate became somewhat slower than the control. The greatest increase was in a case of sinus arrest (Case 20) where the rate rose on one occasion from 60 to 112, and the greatest decrease was in a case of auricular fibrillation, mentioned above, where the ventricular rate suddenly fell to 20.

DISCUSSION

Following parenteral administration, magnesium is at first distributed throughout the extracellular fluids, the ion behaving in this respect like sodium rather than potassium.[2] Few figures are available to show the changes in serum levels in man immediately after administration. Following two or three intramuscular injections of 2 c.c. of 50 per cent magnesium sulfate, the serum level may not exceed 3 mg. per cent (2.5 mEq. per L.).[3] Immediately after intravenous infusion of 500 c.c. of 2 per cent magnesium sulfate over a period of 30 to 60 minutes, levels of 4 to 10 mEq. per L. have been reported.[4] However the latter applies to patients with nephritis whose excretion of magnesium is presumably impaired.

Magnesium is rapidly excreted, and almost entirely by the kidneys. Excretion may be expected to be complete within 4 to 8 hours when renal function is normal.[5] Even after daily injections for long periods of time in dogs[6] and in human beings[7] there is no cumulation in the serum. However, urinary and fecal excretion do not account for all of the administered magnesium. A small part is segregated somewhere in the body, in a location not yet known.[2] Because of the rapid excretion, repeated injections are feasible.

Intravenous infusion of magnesium chloride or sulfate in normal animals causes distinct cardiac effects. With small doses or short infusions the P-R interval increases and the heart rate falls for a short while.[8] With large doses the fall in rate may progress to actual cardiac standstill, which may then be followed by spontaneous resumption of the heart beat.[9,10] The depressant action is not affected by the prior administration of atropine and is therefore presumed to be due to a direct effect upon the myocardium.[11] In addition, there is some evidence that magnesium also has a blocking action upon sympathetic ganglia and that depression of cardio-accelerator impulses may also play a part in producing the slowing.[12]

Smith, Winkler, and Hoff[13] have correlated the electrocardiographic changes in animals with the serum concentrations of magnesium during continuous intravenous infusion of the sulfate. At first (2 to 5 mEq. per L.), there is a transient increase in rate, and shortening of the P-R interval. As the concentration of magnesium rises, these changes are reversed and various grades of auriculoventricular block appear (10 mEq. per L.). Then the QRS widens (12 mEq.

per L.). Finally, (15 mEq. per L.) respiratory arrest occurs concurrent with, or preceding, cardiac arrest. Ectopic rhythms do not arise except in response to cardiac puncture.

The normal human heart responds to the doses of magnesium customarily used (10 to 20 c.c. of 10 to 20 per cent magnesium sulfate, intravenously) with only slight and unimportant changes in the electrocardiogram.[14,15] The serum concentration of magnesium has been raised from 2.8 to 5.2 mg. per 100 c.c. (from 2.3 to 4.3 mEq. per L.) with no resulting electrocardiographic change.[16] Indeed, the only consistent effect of the injection is the flushing action noted by Pines and Kieff[17]: a feeling of intense heat in the throat, radiating downward through the body, and accompanied by visible blushing. Zwillinger[1] suggested the use of magnesium sulfate in measuring circulation time because of this action, and it has been so applied.[18,19] All of our patients had this flushing action, as already stated.

In 1935, Zwillinger[1] reported the successful use of intravenous magnesium sulfate (10 to 20 c.c. of 15 per cent solution) in the abolition of ventricular extrasystoles due to digitalis and strophanthin intoxication in 15 patients. He also reported the protective action of magnesium against digitalis poisoning in frogs and dogs. Similar protective action against strophanthin and barium in dogs was reported by Rothberger and Zwillinger.[9] On the other hand, Smith, Winkler, and Hoff[13] felt that magnesium would not be of value in digitalis intoxication since ventricular tachycardia and fibrillation could be provoked in their dogs despite very high magnesium concentrations. Miller and Van Dellen[20] state that, in general, magnesium sulfate does not overcome toxic digitalis effects in dogs, but may actually increase the degree of block and the occurrence of ectopic impulses. The latter objections are not strictly applicable to clinical cases of digitalis intoxication, as is indicated by our results. The chief reasons why magnesium has little actual value in this condition are its ephemeral action, and its occasional tendency to increase the irregularity.

Ventricular Extrasystoles.—Our results paralleled those of Zwillinger.[1] It will be noted that only one patient with digitalis extrasystoles (Case 45) failed to respond. In addition, all four of our patients with frequent extrasystoles not due to digitalis responded to magnesium. This is at variance with Szekely's experience.[15] The characteristic action of magnesium is to abolish, or strikingly reduce, the extrasystoles almost immediately after injection. The action seldom lasts more than a few minutes. Transient increases in their number occasionally occur, and even a short paroxysm of ventricular tachycardia may appear. These paradoxical effects have been noted during the onset or the offset of magnesium effects.

Zwillinger[1] described a case of ventricular tachycardia due to strophanthin intoxication which progressed to ventricular fibrillation. Cardiac activity was restored by an intracardiac injection of magnesium sulfate. Paroxysms of frequent ventricular extrasystoles recurred five times and each time were temporarily abolished by intravenous magnesium sulfate. After the last injection they were absent for 7 hours, until death. Rothberger and Zwillinger[9]

demonstrated the effectiveness of magnesium in abolishing ventricular tachycardia produced in dogs by strophanthin or barium. Freundlich[21] has reported a case of bidirectional ventricular tachycardia due to digitalis which was temporarily abolished by magnesium. Schwartz[22] has successfully used magnesium to abolish attacks of ventricular tachycardia induced by epinephrine in patients with complete heart block. It has been shown that magnesium sulfate can prevent ventricular tachycardia and fibrillation after large intravenous doses of mercurial diurectics, and its clinical use for this purpose has therefore been suggested.[23] We have not had an opportunity to observe the effects on ventricular tachycardia, or on auricular tachycardia. There are several favorable reports on the latter.[1,15,24,25]

Auriculoventricular Conduction.—The changes during sinus rhythm are not striking and are in accord with previous observations.[26] The increase in grade of auriculoventricular block during auricular fibrillation has also been previously noted.[27]

Sinus Arrest.—The immediate, though transient, abolition of this mechanism by magnesium has not been previously reported. The effect superficially resembles that of intravenous atropine and this resemblance applies also to the magnesium effects on sinus rates in general.

SUMMARY AND CONCLUSIONS

1. Magnesium sulfate was given intravenously (20 c.c. of 20 per cent solution) 29 times to 25 patients with a variety of rhythmic disturbances. The arrhythmias were due to digitalis intoxication in 13 cases.

2. The cardiac effects were rapid in onset, and of very short duration, rarely more than eight minutes.

3. Ventricular extrasystoles, whether due to digitalis or not, were abolished or sharply reduced. In some instances there was a transient increase in their frequency at the beginning or end of magnesium action. In one case there was a short run of bidirectional ventricular tachycardia.

4. Sinus arrests were sharply, though transiently, abolished in two cases.

5. Magnesium effects on auriculoventricular conduction were either not striking (as in sinus rhythm) or not uniform (as in auricular flutter and fibrillation).

6. It is concluded that the therapeutic use of magnesium in arrhythmias is limited by its ephemeral action and by its occasional undesirable effects.

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THE EFFECTS OF POTASSIUM UPON THE HEART, WITH SPECIAL REFERENCE TO THE POSSIBILITY OF TREATMENT OF TOXIC ARRHYTHMIAS DUE TO DIGITALIS

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THIS study was begun after encountering a case of digitalis intoxication in a 58-year-old woman with arteriosclerotic heart disease who was admitted to the hospital in severe diabetic acidosis. She had been receiving 0.2 mg. of digitoxin daily for several months. After correction of her acidosis, frequent multifocal ventricular extrasystoles appeared. These were strikingly abolished by 2 Gm. of potassium chloride orally as shown in Table I (Case 1).

It was then decided to observe the effects of oral potassium salts on a variety of arrhythmias, especially those due to digitalis intoxication. Potassium salts were given 40 times to 31 patients. One of these (Case 44) was a 19-year-old girl without demonstrable heart disease who had ventricular bigeminy for several weeks. The remaining 30 had heart disease of arteriosclerotic, hypertensive, or rheumatic etiology, and all were in mild to moderate degrees of decompensation. The rhythmic mechanisms of the patients in this series were as follows: frequent ventricular extrasystoles, 24 (including auricular fibrillation, 12; sinus rhythm, 9; incomplete auriculoventricular block, 2; salvos of auricular premature systoles, 1); auricular tachycardia with varying block, 1; auricular flutter, 1; auricular fibrillation without extrasystoles, 1; incomplete auriculoventricular block without extrasystoles, 1; and sinus arrest, 3.

Of these 31 patients, the arrhythmias were clearly due to digitalis intoxication in 18, probably or possibly due to digitalis in 9, and not associated with digitalis administration in 4.

METHOD

Potassium was given in single doses chiefly as the chloride, occasionally as equal parts of the chloride and the acetate. Two patients received the salt by stomach tube; the rest took it orally. The dose varied from 2 to 10 Gm. of the salt in 20 per cent solution in simple syrup, syrup of orange, or syrup of citric acid. The latter was the most palatable. Electrocardiograms were made just before the potassium and at intervals of 30 to 60 minutes afterwards.

When ventricular extrasystoles were present their frequency was indicated as a fraction or ratio of the number of such beats among the total number of beats counted. Whenever possible 100 or more beats were counted. Facilities for estimation of potassium levels in the blood were not available. Potassium was not given to any patient known to have renal failure.

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TABLE I. THE EFFECTS OF POTASSIUM

CASE	AURICULAR RHYTHM*	FREQUENCY OF VENTRICULAR EXTRASYSTOLES	30 MINUTES	40 TO 60 MINUTES	1 TO 2 HOURS	2 TO 4 HOURS
1	RSR	18/100	8/100		0/173	
2	AF	52/100			4/100	
3	AF	6/84	2/85	0/50		0/135
4	RSR	28/100		0/100	0/150	
5	AF	28/100		6/100		2/100
5	AF	50/100		15/100	18/100	50/100
6	AF	128/200	56/100	42/100		28/100 20/100
7	AF	42/100	14/100	0/40	0/56	0/50 0/40
10	RSR	32/100	8/100	0/96	0/190	2/100
11	AF	34/100	0/80		0/110	
13	AF	36/100		0/100	0/100	
13	AF	42/100		32/100	0/100	0/100
14	RSR	20/100	24/100		0/550	
15	Salvos of APS	30/100	0/100	0/150		0/50
18	AF	8/100	5/60	0/200	0/100	
19	Incomplete A-V Block	10/100	70/100		12/100	2/200
19	Incomplete A-V Block	12/109	0/90	0/200	1/70	0/200 0/200
22	AF	Bidirectional Ventricular Tachycardia		20/70 21/100		0/155 0/155
22	AF	48/104		8/120		0/350
22	AF	20/120		0/60		0/100
22	AF	29/109			0/200	

UPON VENTRICULAR EXTRASYSTOLES

LATER	REMARKS	DOSE OF POTASSIUM	DIGITALIS
24 hours : rare ventricular extrasystoles	Died 2 days later of pneumonia and uremia. No clinical or ECG signs of hyperpotassemia.	2 Gm. chloride	Digitoxin intoxication
		10 Gm. mixture	Digilanid intoxication
	Ventricular rate fell from 114 to 84 in 30 minutes. Auricular waves increased in size.	10 Gm. mixture	Digitalis leaf intoxication
24 hours : 25/100		10 Gm. mixture	Digitoxin intoxication
		10 Gm. mixture	Digitalis leaf intoxication
	Two days later.	5 Gm. mixture	Stopped 2 days earlier
8 hours : 0/412 24 hours : 50/100	Initially single and paired extrasystoles following alternate normal beats.	10 Gm. mixture	Digitoxin intoxication
24 hours : 13/100		5 Gm. mixture	Digitoxin intoxication
8 hours : 18/100 24 hours : 20/100		5 Gm. mixture	None
	Initially also 33 aberrant but not premature beats in the 100 counted. These disappeared with the extrasystoles.	10 Gm. mixture	Digoxin intoxication
		10 Gm. chloride	Digitoxin intoxication
8 hours : 0/100 24 hours : 30/100	Initially, occasional trigeminal groups due to pairs of extrasystoles.	10 Gm. chloride	Stopped 2 days earlier
18 hours : 18/100	Initially, several trigeminal groups due to pairs of extrasystoles.	10 Gm. mixture	None
24 hours : 13/100	Short bouts of auricular tachycardia from 2 foci These and all auricular premature systoles abolished in 30 minutes.	10 Gm. mixture	Digitoxin intoxication
6 hours : 1/120	Ventricular rate slowed from 90 to 62 in 2 hours.	10 Gm. mixture	Digoxin intoxication
8 hours : 8/133	Sudden increase in ventricular extrasystoles 23 minutes after potassium, lasting ½ hour.	10 Gm. chloride	Digitoxin intoxication
	Four days later.	10 Gm. chloride	
24 hours : 86/150	Vomited after 10 Gm. potassium chloride. Bidirectional extrasystoles appeared in 24 hours.	10 + 5 Gm. chloride	Digilanid intoxication
6½ hours : 6/100	Two days later. Bidirectional extrasystoles present initially.	10 Gm. chloride	Two days after stopping Digilanid
	One day after above. Bidirectional extrasystoles present initially.	10 Gm. chloride	Three days after stopping Digilanid
18 hours : 16/100	Three days after above. Bidirectional extrasystoles present initially.	10 Gm. chloride	Six days after stopping Digilanid

TABLE I. THE EFFECTS OF POTASSIUM

CASE	AURICULAR RHYTHM*	FREQUENCY OF VENTRICULAR EXTRASYSTOLES	30 MINUTES	40 TO 60 MINUTES	1 TO 2 HOURS	2 TO 4 HOURS
24	RSR	50/100			20/100	3/150 0/150
24	RSR	16/100		0/50		0/100
26	ST	19/70	0/40		0/200	
28	Incomplete A-V Block	26/100		0/100		0/100
29	AF	24/100		0/100	0/250	0/100
31	RSR	16/100		2/100	0/60 0/50	0/110
32	AF	51/200		3/84	0/40	0/100
33	RSR	78/200	14/20	0/50	0/354	0/50
44	RSR	60/120		9/33	16/70	25/100 50/100
44	RSR	100/200		28/100		12/100 50/100
45	AF	28/100		30/100	8/100	

*RSR, regular sinus rhythm; AF, auricular fibrillation; APS, auricular premature systoles; ST, sinus tachycardia.

The frequency of extrasystoles appears in the left, center, or right side of each column according to the time the observations were made with regard to beginning, middle, or end of the observation periods stated at the head of each column.

Fourteen patients had received magnesium[1] prior to potassium. In no instance was the latter given within an hour of the dissipation of all magnesium effects, and in several cases it was given a day or more after the magnesium.

RESULTS

Vomiting occurred three times, in previously nauseated patients, 10 to 20 minutes after ingestion of the solution. One patient was given no additional salt. The other two patients were given 3 and 5 Gm. of potassium chloride with aluminum hydroxide gel immediately after the vomiting and successfully retained it. In all three patients a clear potassium effect was obtained.

1. *Ventricular Extrasystoles.*—In each trial the extrasystoles were abolished or greatly diminished, as shown in Table I and Figs. 1, 2, and 3.

The diminution in frequency of extrasystoles rarely was definite in less than thirty minutes, was maximal usually in one to two hours, and persisted for at least four hours in all but three trials in two patients. Occasionally, the effects lasted for more than eight hours, and rarely for twenty-four hours.

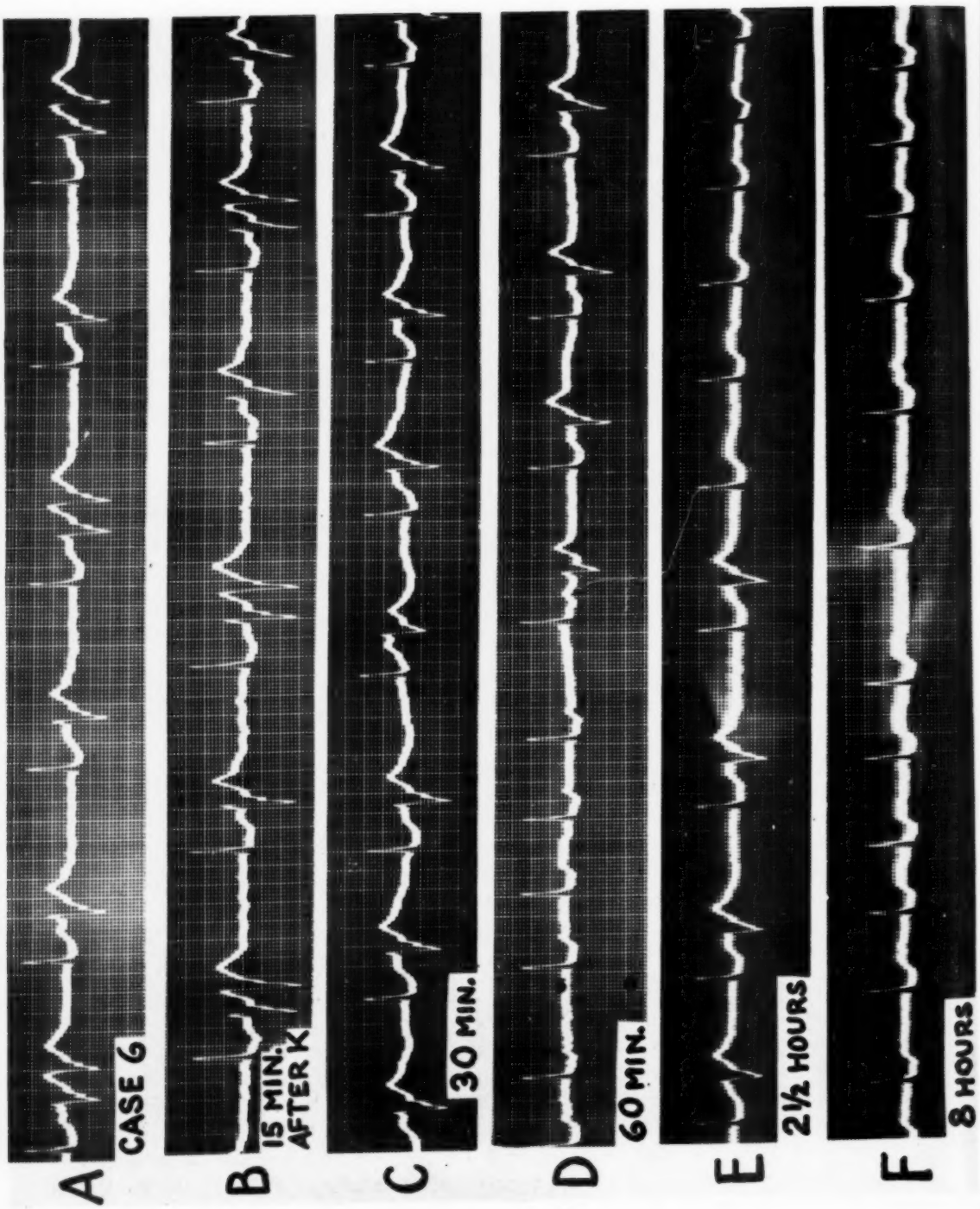
U PON VENTRICULAR EXTRASYSTOLES—(CONTINUED)

LATER	REMARKS	DOSE OF POTASSIUM	DIGITALIS
	T wave negativity increased 1 mm. in 1 hour.	5 Gm. chloride	None
	Five days later.	5 Gm. chloride	None
	Sinus tachycardia, rate 130, fell to 80 in 2 hours.	5 Gm. chloride	Digoxin intoxication
6 hours : 50/100	P-R increased from 0.44 to 0.46 second in 1 hour, then shortened.	5 Gm. chloride	Digilanid intoxication
		10 Gm. chloride	Digoxin intoxication
22 hours : 9/90		10 Gm. chloride	Digoxin intoxication
	In 24 hours normal sinus rhythm appeared (!)	10 Gm. chloride	Digitalis leaf intoxication
24 hours : 20/100	Two auricular extrasystoles appeared in 1½ hours.	10 Gm. chloride	Digilanid intoxication
		5 Gm. chloride	None
	Three days later.	10 Gm. chloride	None
8 hours : 12/100		10 Gm. chloride	Digitalis leaf intoxication

In one instance (Case 19) the frequency of extrasystoles increased temporarily from 10/100 to 70/100 due to the appearance of trigeminy and quadrigeminy caused by consecutive bidirectional extrasystoles. Subsequently, all extrasystoles were abolished. Four days later, while digitalis was still being continued, there was only the usual response to a second trial of potassium.

While recording the electrocardiogram prior to administration of potassium, a patient with frequent ventricular extrasystoles (Case 22) due to Digilanid intoxication suddenly developed several paroxysms of bidirectional ventricular tachycardia. He was given 10 Gm. of potassium chloride but vomited in ten minutes. Five more grams were given, mixed with aluminum hydroxide gel, and this was retained. The paroxysms and the extrasystoles were abolished as shown in Fig. 4 and Table I. In the next week, potassium was given three more times with good results (Table I and Fig. 3).

2. *Auricular Tachycardia.*—The abnormal mechanism was abolished in two patients. The first patient (Case 9) had auricular tachycardia with varying auriculoventricular block which appeared while he was taking a daily maintenance dose of 0.5 mg. of digoxin, and was preceded 24 hours earlier by frequent auricular premature beats. During the tachycardia the auricular rate was 176, the ventricular rate 150. One-half hour after 5 Gm. of potassium chloride-acetate mixture was given there was a sinus tachycardia at a rate of 125. In the next four and one-half hours the rate slowed to 107 and remained in the neighborhood of 100.


A
CASE 6
B
15 MIN.
AFTER K
C
30 MIN.
D
60 MIN.
E
2½ HOURS
F
8 HOURS

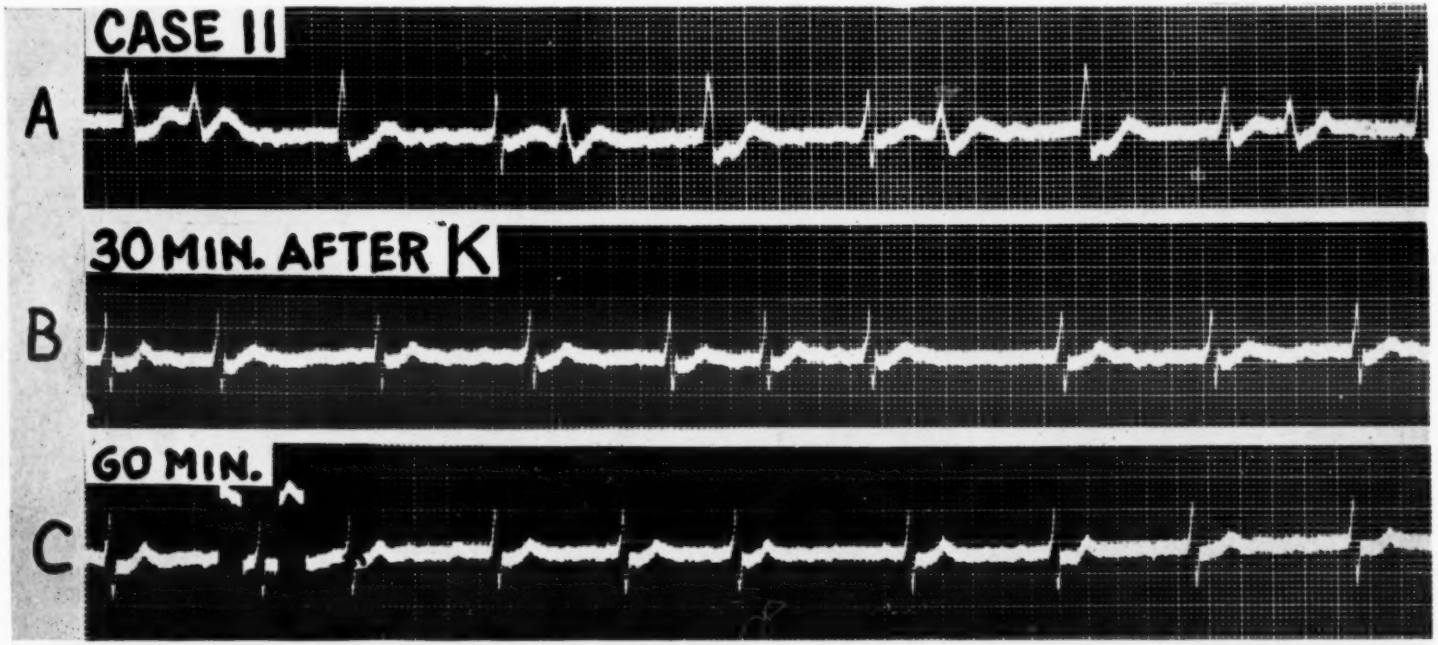


Fig. 2.—Lead II. Potassium effects upon ectopic ventricular beats. *A*. Every third complex is aberrant in form, but not premature. The first complex in the strip is also abnormal in form. *B*. All abnormal complexes, both premature and nonpremature, are abolished.

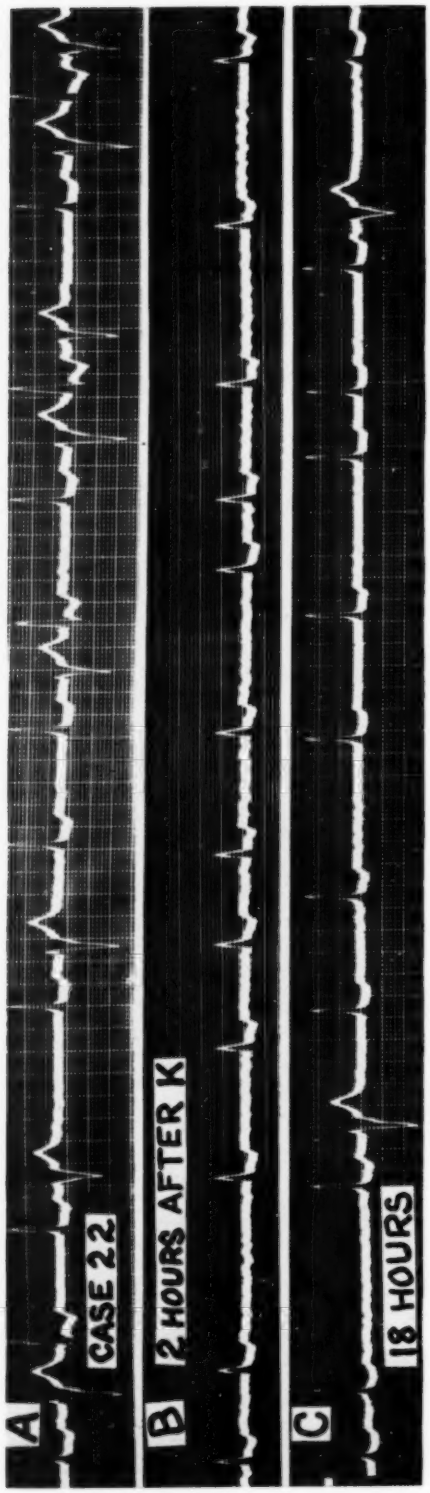


Fig. 3.—*A*. Lead I. Six days after discontinuance of Digitalid. *B*. Lead II. No extrasystoles were present in 200 successive beats. *C*. Lead I. The patient had paroxysms of ventricular tachycardia six days earlier (Fig. 4).

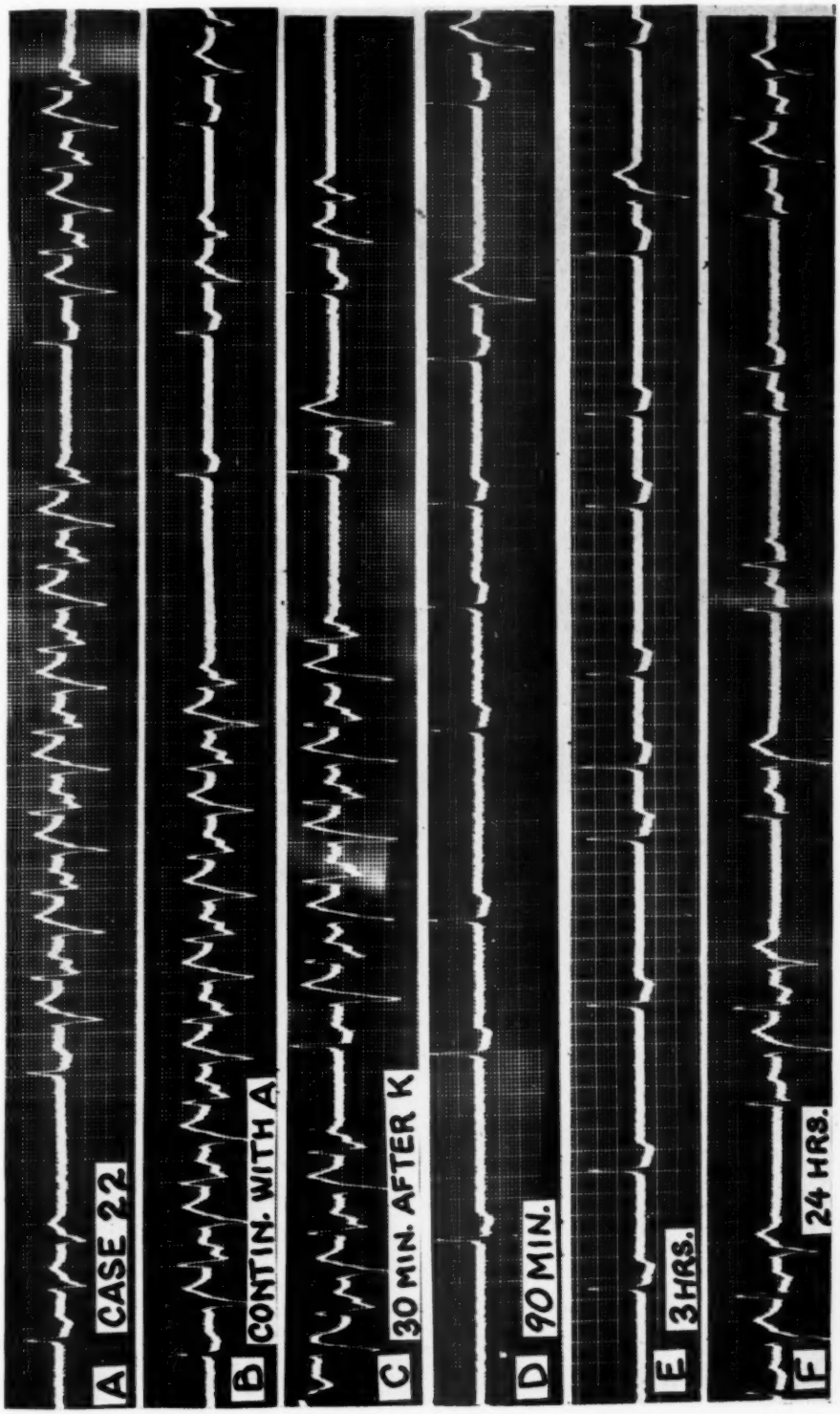


Fig. 4.—Abolition of bidirectional ventricular tachycardia. The height of action occurred in two hours, when there were 155 successive beats without an extrasystole.

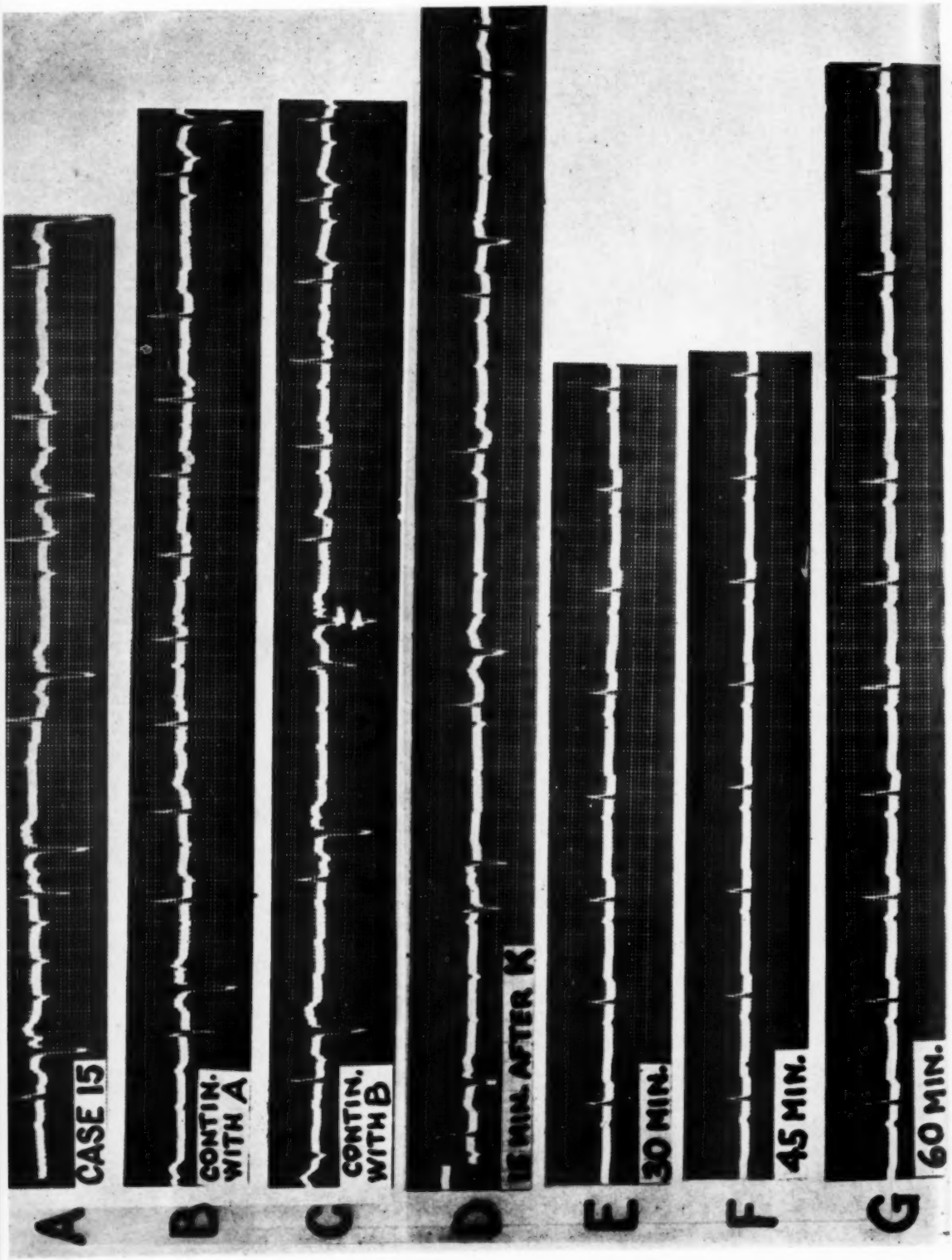


Fig. 5.—Response of a patient with bidirectional auricular tachycardia with varying auriculoventricular block and frequent ventricular extrasystoles.

The second patient (Case 15, Table I, and Fig. 5) had ventricular bigeminy associated with salvos of auricular premature beats from two foci, actually constituting short runs of tachycardia. We have therefore termed the rhythm bidirectional auricular tachycardia. The response to 10 Gm. of the potassium chloride-acetate mixture was dramatic, all abnormal mechanisms being abolished in thirty minutes.

3. *Auricular Flutter.*—In a patient with a ventricular rate of 110, after 10 Gm. of the chloride-acetate mixture, the rate slowed to 80. The slowing appeared in forty minutes and lasted at least four hours. The auricular rate was not affected.

4. *Auricular Fibrillation.*—In a patient with no extrasystoles the ventricular rate fell from 72 to 50 following 5 Gm. of potassium chloride. The slowing appeared in forty-five minutes, was maximal in two and one-half hours, and wore off within four hours. At the time of greatest slowing the ventricular rhythm became more irregular due to frequent long pauses. Auricular deflections increased in amplitude but the rate was not perceptibly altered.

In another instance (Case 32, Table I) auricular fibrillation reverted to sinus rhythm twenty-four hours after the potassium was taken.

5. *Incomplete Heart Block.*—Two patients with, and one without, extrasystoles received potassium. They all showed definite increase of the P-R interval or development of dropped beats. These effects lasted up to three hours.

6. *Sinus Arrest.*—In two patients the sinus arrests occurred more frequently, the action persisting up to eight hours. In the third patient the escape mechanism became perpetuated (Case 8, Fig. 6).

7. *Auriculoventricular Conduction and Heart Rate.*—There was no clear effect on patients with normal sinus rhythm, but in general there was slight to moderate slowing of the ventricular rate in auricular fibrillation presumably due to an increase in the grade of auriculoventricular block.

8. *T Waves.*—There was no change in size or shape of a magnitude sufficient to be detected without careful measurement. In no case was there a change in direction of a T wave, nor in position of an RS-T segment. These statements apply to the standard limb leads only. Precordial leads were made after potassium administration in only a few instances.

DISCUSSION

Potassium is rapidly absorbed from the gastrointestinal tract, but the serum level increases slightly, if at all, after moderate doses. The potassium ion is highly mobile, readily migrating across the cell boundaries.[2] When potassium is injected into the veins of cats it diffuses so rapidly from the plasma into the tissues that it requires several minutes for the plasma concentration to rise.[3] This may account in part for the slight increases in blood concentrations of potassium following the administration of moderate doses to human subjects with

Fig. 5.—Response of a patient with bidirectional auricular tachycardia with varying auriculoventricular block and frequent ventricular extrasystoles.

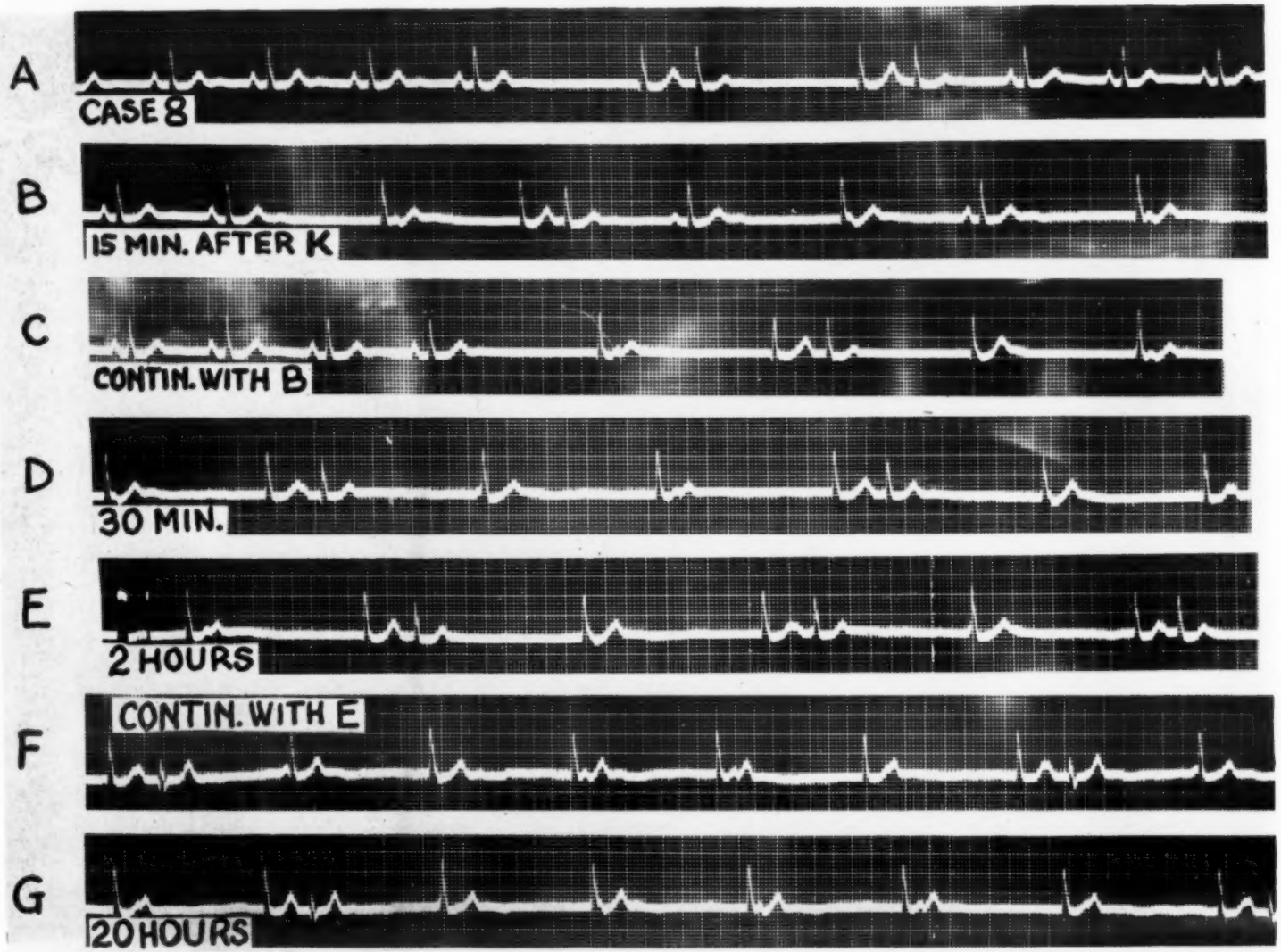


Fig. 6.—Perpetuation of the escape mechanism in a patient with frequent sinus arrests. The condition was exactly reproduced four months later, and

adequate renal function. Large amounts are required to result in an increase of the serum concentration even after intravenous infusion provided there is no renal failure.[4] It is difficult to produce a rise of more than 3 mEq. per L. by oral administration; doses as high as 10 Gm. of potassium chloride in man increase the serum level only 1 to 2 mEq. per L.[5] Increases of this magnitude were reported in Sampson's[6] group of patients, most of whom received 5 Gm. of potassium acetate. In this group the serum concentration rose in one-half hour, reached a peak in about one and one-half hours, and returned to normal after two to two and one-half hours.

Excess potassium is readily excreted except in the presence of renal failure. Keith, Osterberg, and Burchell[7] showed that doses as high as 17.5 Gm. of the chloride can be tolerated without evidence of toxicity even in the presence of renal disease. In fact, it may even act as a diuretic. However, there are reports of toxic concentrations following potassium administration in the presence of mild or moderate renal disease.[8] Obviously, in acute renal failure, terminal uremia, and severe passive congestion of the kidneys, it may be dangerous. Paresthesias constitute the clinical sign of a toxic level.

Slow, continuous intravenous infusion of potassium chloride in animals results in uniform electrocardiographic changes; first increased height of T waves, then intraventricular block, disappearance of P waves, and finally cardiac arrest.[5] This sequence of events is well duplicated in experimental anuria, in which the concentration of serum potassium rises progressively because of tissue breakdown, inability to store potassium, and inability to excrete the ion.[9]

The common salts of potassium in moderate dosage have little effect upon the normal human heart. Harris and Levin[4] found slight slowing of the rate as the only consistent change. In toxic concentrations, however, as in the presence of renal failure, the characteristic high peaked T waves and prolonged QRS complexes may occur.[10] The opposite effect on the T waves has been often noted in conditions associated with abnormally low serum concentrations of potassium as in Addison's disease,[11] protracted vomiting,[12] and diabetic acidosis.[1, 14] Thomson[11] suggested that the height of the T wave might serve as a guide to the serum potassium level, and in some individual patients this has been found to be of value.

Arrhythmias have been reported in conjunction with abnormally low concentrations of potassium[12] as well as during the administration of potassium salts.[15] The latter is not a commonly encountered situation. Our interest in the relation of potassium to arrhythmias is in its effects upon established abnormal rhythms. Sampson and Anderson[16] in 1932 reported the correction of 29 out of 58 instances of extrasystoles with oral potassium salts in doses of from 1 to 15 Gm. One patient with ventricular tachycardia also responded favorably. In 1943, Sampson, Alberton, and Kondo[6] succeeded in abolishing or greatly diminishing the extrasystoles due to digitalis excess in all 13 of their patients with this toxic rhythm. In their review of the literature they pointed out the lack of agreement of various workers in regard to the influence of potassium upon therapeutic doses of digitalis. However, they noted the consensus that toxic doses of digitalis are associated with a loss of potassium from myocardial

Fig. 6. Perpetuation of the ectopic mechanism by a patient with frequent ulnar arrests. The condition was nearly reproduced four months later, and

cells. A recent study[17] indicates that potassium offsets digitalis toxicity by directly reducing the irritability of the heart and by replacing the potassium loss which probably occurs when the heart is exposed to toxic amounts of digitalis.

1. *Ventricular extrasystoles.*—The relation of potassium to extrasystoles is very interesting. Castleden[18] demonstrated a fall in serum potassium following epinephrine administration, and subsequently succeeded in reducing the ventricular extrasystoles caused by epinephrine in a patient by giving potassium an hour before the epinephrine. He also used potassium to prevent extrasystoles in a diabetic patient who had extrasystoles associated with hypoglycemia due to insulin, and in addition abolished the extrasystoles in another patient with digitalis intoxication. Thus, potassium was effective in reducing extrasystoles due to epinephrine administration, insulin administration, and digitalis excess. Each of these factors is known to result in a potassium loss. The potassium may work by directly depressing conductivity and increasing refractoriness; by replacement of the deficient ion in the heart muscle; by altering the hydrogen ion concentration; or by affecting the calcium-potassium ratio in the myocardial cell.[19]

It is conceivable that our Case 1 developed spontaneous digitalis intoxication because of a fall in potassium consequent to treatment for diabetic acidosis. Unfortunately, no potassium estimations were made. It may be useful, in future, to test the tolerance to digitalis of patients in a state of potassium depletion. If toxic rhythms should appear after unusually small amounts of digitalis, they should be favorably affected by potassium. In the series of Sampson and co-workers,[6] there was no correlation between the occurrence of extrasystoles and the serum potassium level. However, all his patients had normal levels and their extrasystoles were due to large amounts of digitalis.

Our results are in complete accord with those of Sampson and his co-workers.[6] In every case of digitalis toxicity ventricular extrasystoles were abolished or greatly diminished, usually for a period of several hours. Sampson and Anderson[16] reported three instances of paradoxical potassium effect, that is, an increase in the number of extrasystoles, all in nondigitalized persons. Only one such event occurred in our group (Case 19, digitalis intoxication). It will be noted that four of our patients had received no digitalis, yet responded to potassium as the digitalis-toxic patients did.

2. *Ventricular Tachycardia.*—Several instances of ventricular tachycardia associated with coronary disease have been successfully treated with potassium salts.[16,20,21] Indeed, Kerr[21] states that potassium is preferable to quinidine in the ordinary patient with this arrhythmia. Our Case 22 responded so strikingly that we feel potassium may well be the agent of choice in the treatment of ventricular tachycardia caused by digitalis intoxication.

3. *Auricular Tachycardia.*—Potassium has been reported to be effective,[16] but we are not aware of other reports on its use in a group of patients. Two of our patients had auricular tachycardia presumably due to digitalis toxicity. Case 15 had what we prefer to term bidirectional auricular tachycardia. Sinus rhythm was restored thirty minutes after potassium was given. Case 9 had

auricular tachycardia with varying block which was replaced by a sinus tachycardia thirty minutes after potassium was given. It has been shown that potassium has a depressant action upon all properties of auricular muscle,[22] and this may possibly explain its effect.

4. *Auricular Fibrillation.*—Three patients with paroxysmal fibrillation have been reported as being restored to normal rhythm by repeated doses of potassium.[23] However, it is difficult to prove that the paroxysms were actually terminated by this agent since restoration occurred hours after the start of therapy. The same objection applies to our Case 32, where the likelihood is that reversion occurred spontaneously.

5. *Sinus Arrest.*—The results are in accord with the view that potassium depresses the rate of impulse formation and conduction, and increases refractoriness in the auricle.

6. *Auriculoventricular Conduction and Heart Rate.*—Recognizable increase in auriculoventricular conduction time occurred only in patients with some degree of existing block. Similar clinical observations have been noted.[6,24]

7. *T Waves.*—Potassium effects on T waves are known to be striking in conditions with abnormal concentrations of the ion.[11,24] A very interesting finding was reported by Sharpey-Schafer[25]: after 15 to 20 Gm. of potassium chloride-acetate mixture the inverted T waves due to left ventricular preponderance became upright, while the inverted T waves due to infarction became deeper. We found no similar changes in our patients, possibly because the doses used were one-third to one-half as large. Goldberger and his associates[26] reported striking changes in the precordial T waves of normal children, but the doses were relatively large. As previously stated, the T wave changes in our series were not impressive, though it should be repeated that only the limb leads were available for comparison.

SUMMARY AND CONCLUSIONS

1. Potassium salts (2 to 10 Gm. of the chloride or of chloride-acetate mixture) were given forty times to 31 patients with various arrhythmias, mostly associated with digitalis.

2. Clear effects occurred in each trial, appearing in about one-half hour and persisting for at least four hours.

3. Ventricular extrasystoles were uniformly reduced or abolished.

4. One patient with bidirectional ventricular tachycardia was successfully treated.

5. Two patients with auricular tachycardia were restored to normal rhythm.

6. In general, conduction disturbances were worsened.

7. It is concluded that potassium salts may have therapeutic application in some arrhythmias, particularly certain toxic rhythms due to digitalis intoxication.

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RESULTS OF TREATMENT OF CORONARY ARTERIOSCLEROSIS WITH CHOLINE

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THE purpose of this report is to describe the results of treatment of coronary arteriosclerosis using the lipotropic agent, choline, in patients having proved coronary thrombosis and myocardial infarction.

Previous papers by one of us (L.M.M.) and his co-workers have reported further evidence for the concept that disorders in lipoid metabolism are important factors in the development of arteriosclerosis.[1-6] Recently, we have shown that abnormal elevations in blood serum cholesterol occur in the majority of patients with coronary thrombosis[1] and that choline can effect the absorption of established atherosclerosis in the experimental animal.[2] These observations were also reported by other investigators.[7-9]

The authors have recently shown that in a series of over 600 patients studied in detail, elevation in blood serum lipids was associated with increased rate and degree of arteriosclerosis affecting the coronary arteries and the aorta; conversely, it was shown that a subnormal or low serum lipid content was associated with a decreased rate and degree of coronary and aortic arteriosclerosis.[5]

Choline has been shown to be an effective lipotropic (fat-preventing) agent both experimentally and clinically.[10] This member of the vitamin B complex has also been shown to be effective in both preventing and absorbing atherosclerosis in the experimental animal. Recent reports have also appeared describing the clinical value of the lipotropic agents choline and inositol (another member of the vitamin B complex) in the treatment of human arteriosclerosis.[17,18]

Three years have now elapsed since the authors began a controlled investigation into the use of choline in arteriosclerosis, and it was felt that a description of preliminary impressions would be of interest.

Because of the difficulty in evaluating therapeutic results in a disease such as arteriosclerosis, subject as it is to such wide variations in diagnostic accuracy, possible doubts as to clinical significance of symptoms, and differences between atheromatosis (a clinical entity) and arteriosclerosis of the medial calcinosis type (of dubious clinical significance),[19] we felt that only proved cases of this disease would be acceptable for study. Therefore, only patients who had indisputable evidence of a coronary thrombosis with myocardial infarction were selected for this study since these conditions are due to coronary arteriosclerosis.

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Accordingly, a series of 115 patients treated with choline is herein described. These patients had proved coronary thrombosis indicated by typical serial electrocardiograms and clinical history; they had survived the acute episode of occlusion and were discharged from the hospital six weeks from the date of their admission. A series of patients with similar proved coronary thrombosis who did not receive choline treatment served as the control subjects since they were alternate unselected patients who had entered the hospital under the same conditions. These patients had survived their acute episode and were also discharged under the same conditions. The dosage which was first employed was aimed at a maximum of 32 grams daily by mouth, since the senior author as well as other investigators have shown that in experimental atherosclerosis the most effective therapeutic results in prevention or absorption of the atheromatous lesions are achieved when the maximal dose which the animal can tolerate is ingested.[2] However, many patients were unable to take this dose of 32 grams daily for prolonged periods of time and a small percentage were unable to tolerate any amount of choline due to the ensuing gasteroentritis. The minimum dosage taken was 6 grams daily of the choline in the form of the bicarbonate salt, and the average oral dose for most patients was 12 grams daily. Occasional minor but unpleasant side reactions occurred—mostly manifestations of gastroenteritis, vertigo, or body odor.

The treated and the control patients had been treated in identical manner, with the currently used standard methods of bed rest, palliative therapy, morphine, a hospital select diet, and, in the past one and one-half years, routine administration of Dicumarol to every patient. After the patients were discharged from the hospital they either attended the special research clinic in the outpatient department of the hospital for choline treatment or they were observed as control patients who did not receive choline or who, in certain cases, were being treated in the cardiac or medical clinic by digitalis, low sodium diet, and other palliative medical therapy.

The ages of the patients treated with choline ranged from 28 to 70 years with an average of 58 years. Those not treated with choline ranged from 30 to 70 years. Of the 115 choline-treated patients, 17 were female, 98 were male patients. Of the 115 noncholine treated patients, 21 were female, 94 were male patients. Blood serum lipid studies including serum cholesterol and esters, phospholipids, esterases, total lipids, lipo-protein relationships, iodine metabolism, liver function tests, fat tolerance tests, and other studies were, and still are, being carried out with these subjects as part of metabolic surveys which are being reported separately.

Of all choline-treated and nontreated control patients, only those were included in this report who had had their first coronary occlusion, in order to avoid variable factors in the analysis.

The choline-treated patients fell into three groups. Group 1 consisted of 52 patients who received choline daily for one year. Group 2 consisted of 35 patients who received choline daily for two years. Group 3 comprised 28 patients who took choline daily for three years. Most of these patients took

TABLE I. SUBSEQUENT YEARLY SURVIVAL RATE IN 115 PATIENTS TREATED WITH CHOLINE FOLLOWING A SIX-WEEK RECOVERY FROM ACUTE ATTACK OF CORONARY THROMBOSIS

GROUP	PERIOD OF OBSERVATION (YEARS)	NUMBER OF PATIENTS	DEATHS DURING THE YEAR
Group 1. One-Year Period of Choline Treatment	1	52	4
Group 2. Two-Year Period of Choline Treatment	1	35	3
	2	32	2
Group 3. Three-Year Period of Choline Treatment	1	28	2
	2	26	2
	3	24	1

their daily dosage regularly except for occasional lapses of an unavoidable nature due to intercurrent noncardiac illnesses, employment or transportation difficulties, and the like.

We have summarized in Table I the mortalities of the patients who received choline treatment after their discharge from the hospital following recovery and in Tables V and VI the causes of death which were cardiac in most patients. It is noted in Group 1 of Table I that 4 patients of the 52 under treatment died at the end of the first year following their hospital discharge for the initial attack of coronary thrombosis. Group 1,A, Table II reveals a comparison of the mortalities in 52 control subjects who did not receive choline treatment. Ten of these patients died at the expiration of one year. In Group 2 (Table I) of 35 patients who received choline for two years, 3 died at the end of one year as compared with 7 deaths among 35 control patients who did not receive choline and who were observed over the one year period in Group 2,A (Table II). Furthermore, in this same group of the choline-treated patients, 32 survived in the

TABLE II. SUBSEQUENT YEARLY SURVIVAL RATE IN 115 NONCHOLINE-TREATED CONTROL SUBJECTS FOLLOWING A SIX-WEEK RECOVERY FROM ACUTE ATTACK OF CORONARY THROMBOSIS

GROUP	PERIOD OF OBSERVATION (YEARS)	NUMBER OF PATIENTS	DEATHS DURING THE YEAR
Group 1, A. One-Year Period of Observation	1	52	10
Group 2, A. Two-Year Period of Observation	1	35	7
	2	28	5
Group 3, A. Three-Year Period of Observation	1	28	5
	2	23	4
	3	19	4

second year; 2 of these patients died within the second year. In comparison, 28 patients of the noncholine-treated control patients survived in the second year from the original 35, and 5 of these had died at the expiration of the second year of observation (Table II).

In Group 3 (Table I) 28 patients were to be treated with choline for three years. Two died at the expiration of one year. In comparison, Group 3,A (Table II) reveals that of 28 noncholine-treated control patients who were observed for three years, 5 died at the end of one year. Of the 26 choline-treated patients who survived (Group 3) to undergo treatment in the second year, 2 died at the end of the year as compared to 4 patients who died in the control group (3,A) of 23 patients under comparable conditions. Finally, in Group 3 of the 24 choline-treated patients who survived the second year to enter the third year of treatment, 1 patient died at the end of the third year of choline treatment compared to 4 control patients who died in Group 3,A out of 19 control subjects who were observed in the third year without choline.

A comparison is made of the total mortality rate in Table III between the 115 choline-treated patients with 14 deaths at the end of the three-year period and 115 noncholine-treated subjects with 35 deaths at the end of the three-year observation period. This latter mortality rate in the noncholine-treated series is comparable to those reported by previous observers.[22-24]

TABLE III. COMPARISON OF SURVIVAL RATES OF PATIENTS WITH CORONARY THROMBOSIS WITH AND WITHOUT CHOLINE TREATMENT AFTER THREE YEARS

Deaths in 115 Choline-Treated Patients: 14	Deaths in 115 Noncholine-Treated Patients: 35

Recently, Levine[22] reported that after recovery from acute coronary thrombosis had taken place, one-fourth of the patients died within one year, one-half died within two years and three-fourths were dead within five years. Bland and White[23] found a lower mortality rate which ranged from 15 to 20 per cent each year for the first three years. Our mortality figures in the noncholine-treated patients are more in keeping with those of Bland and White although not very far off from those of Levine.

TABLE IV. CONDITION OF 230 CORONARY THROMBOSIS PATIENTS EIGHT WEEKS AFTER DISCHARGE FROM THE HOSPITAL

CHOLINE	SYMPTOM FREE ON EXERTION	ACTIVITY CURTAILED BY ANGINA PECTORIS	ACTIVITY CURTAILED BY DYSPNEA
Patients Not Given Choline After Discharge (Total: 115)	43 (38 per cent)	38 (33 per cent)	34 (29 per cent)
Patients Given Choline After Discharge (Total: 115)	46 (40 per cent)	31 (27 per cent)	38 (33 per cent)

Table IV describes the conditions of 115 patients before choline treatment approximately six weeks following their discharge from the hospital after recovery from the acute coronary thrombosis. It is there seen that 43 patients (38 per cent) of the 115 patients were symptom free and noted no distress or abnormality on the resumption of physical exertion. However, it is to be borne in mind that many of these patients may have had an unconscious avoidance of any undue or, for them, normal physical activity due to fear of heart strain. Thirty-eight patients (33 per cent) complained of angina pectoris and 34 (29 per cent) noticed dyspnea on exertion. For comparison Table IV also describes the condition of 115 patients who did not receive treatment with choline subsequently. Forty-six patients (40 per cent) were symptom free on physical exertion, 31 patients (27 per cent) noted angina pectoris, and 38 patients (33 per cent) complained of dyspnea on exertion.

In the above three "recovery" types of 115 control patients not treated with choline the mortality rate and cause of death are described in Table V after three years. Here it is seen that of the 43 patients who were asymptomatic following their hospital discharge 9 had died of recurrent coronary thrombosis, 1 was dead of cardiac congestive failure, 2 had died of noncardiac causes, and 1 patient could not be traced. Of the 38 patients who had angina pectoris, 7 had died of recurrent coronary thrombosis, 1 died of cardiac congestive failure, 1 died of extracardiac cause, and 2 cases could not be located. Of the 34 patients who had dyspnea on exertion 3 were dead of recurrent coronary thrombosis, 6 died in cardiac congestive failure, 1 died of extracardiac cause, and for 1 the cause of death was unknown. In comparison, Table VI describes the mortality rate and cause of death in the three "recovery" types of 115 patients treated with choline for three years. Of 46 asymptomatic patients 2 had died of recurrent coronary thrombosis and 1 had died of noncardiac causes. Of 31 patients with angina pectoris 3 had died of recurrent coronary thrombosis. In 38 patients with dyspnea on exertion there was 1 death due to recurrent coronary thrombosis, 5 deaths due to congestive heart failure, 1 death from noncardiac cause, and 1 death of which the cause was unknown.

TABLE V. CAUSE OF DEATH IN 115 NONCHOLINE-TREATED CORONARY THROMBOSIS PATIENTS AFTER THREE YEARS OF TREATMENT

TYPE	NUMBER OF PATIENTS	PER CENT	RECURRENT CORONARY THROMBOSIS	CARDIAC CONGESTIVE FAILURE	EXTRA-CARDIAC CAUSE	NOT TRACED	TOTALS
Patients who were symptom free on exertion	43	38	9	1	2	1	13
Patients whose activity was curtailed by angina pectoris	38	33	7	1	1	2	11
Patients whose activity was curtailed by dyspnea	34	29	3	6	1	1	11
Totals	115	100	19	8	4	4	35

Thirty-eight (33 per cent) of the choline-treated patients were hypertensive patients having a persistent systolic blood pressure over 150 mm. Hg and a persistent diastolic pressure of over 100 mm. Hg. The control series had 34 hypertensive patients (30 per cent).

TABLE VI. CAUSE OF DEATH IN 115 PATIENTS WITH CORONARY THROMBOSIS TREATED WITH CHOLINE AFTER RECOVERY FROM ACUTE ATTACK OVER THREE-YEAR PERIOD

TYPE	NUMBER OF PATIENTS	PER CENT	RECURRENT CORONARY THROMBOSIS	CONGESITVE HEART FAILURE	NON-CARDIAC ILLNESS	UN-KNOWN	TOTALS
Patients who were symptom free on exertion	46	40	2		1		3
Patients whose activity was curtailed by angina pectoris	31	27	3				3
Patients whose activity was curtailed by dyspnea	38	33	1	5	1	1	8
Totals	115	100	6	5	2	1	14

COMMENT

Although previous studies[17,18] have reported successful results with the use of lipotropic agents in arteriosclerosis and coronary artery disease, no control studies were available and the diagnostic criteria employed did not appear to be of a sufficiently precise nature to permit a satisfactory evaluation of these lipotropic agents. The criteria adopted in this investigation of accepting for treatment and control subjects only those patients with indisputable evidence of acute coronary thrombosis with myocardial infarction established the existence of coronary arteriosclerosis and would appear to overcome the objections stated above.

Although a number of hypotheses of the mode of action of choline have been offered, such as an increase in the rate of phospholipid turnover by the liver, or the action of choline as a catalyst in the "burning of fats" in the liver, etc., still the action of choline remains unexplained. In this respect choline is not unlike various other recently discovered vitamins or vitamin-like substances whose exact physiological mechanisms at present are unknown. Recent studies[20] have demonstrated that various components of the vitamin B complex enter into the formation of enzymes that play an essential part in intestinal phosphorylation and absorption. It may be that the action of choline is mediated in this way in the small intestinal mucosa. Recently, Chaikoff[21] has shown that oxidation takes place independently within the arterial wall itself. The possibility of the catalytic action of choline in the artery on the combustion of fats appears to merit consideration. Experimental studies in animals have shown that when atherosclerosis is produced, choline may prevent or actually absorb the atheromatous lesions in the artery itself. These studies may suggest a similar possi-

bility with respect to the coronary arteries of some of the patients reported in this study in whom favorable therapeutic results were suggested.

Studies, previously reported by the author, on experimental animals have indicated that in experimental atherosclerosis, the most effective therapeutic results were obtained in absorption of the atherosclerosis when a maximum tolerated dose was ingested by the animal. In our human series of patients this dose appeared to be 32 grams of choline daily. This dose was taken by a few patients over a two- to three-year period of time with striking therapeutic results. In those patients able to tolerate such large choline intake, who were free of congestive cardiac failure, none experienced a recurrent coronary thrombosis and some lost completely any anginal pain that had been present.

These as well as other clinical observations of interest will be discussed in detail in a separate communication.

We have used the lipotropic agent inositol, another vitamin-like member of the vitamin B complex alone and in combination with choline in a series of patients with coronary arteriosclerosis and will describe these after a prolonged period of controlled observation.

SUMMARY

1. A series of 115 patients with proved coronary thrombosis and myocardial infarction were treated with choline for periods of one to three years after recovery from the immediate attack. These patients were compared to 115 control patients who were alternately admitted to the hospital with the same diagnosis but who did not receive choline treatment.

2. The dosage of oral choline averaged 12 grams daily. It was taken for one year by 52 subjects, for two years by 35 subjects and for three years by 28 subjects.

3. The subsequent mortality rate of patients who had suffered an acute coronary thrombosis with myocardial infarction appeared to be significantly reduced by the treatment with choline in this series of patients.

4. These studies suggest that the lipotropic agent choline is of value in the treatment of coronary arteriosclerosis and would appear to merit further trial and observation in this disease.

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THE INFLUENCE OF INSULIN SHOCK THERAPY ON THE ELECTROCARDIOGRAM

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IT HAS been established that hypoglycemia may have a transient effect upon the heart and circulation. This conclusion is based not only upon the observed effect of moderate grades of hypoglycemia in patients with myocardial disease but also upon the electrocardiographic changes observed in normal hearts following insulin shock therapy. Previous electrocardiographic studies during insulin shock in the presence of myocardial disease, have revealed inversion of the T waves, extrasystoles, auricular fibrillation, disturbances in the auriculoventricular conduction, and lengthening of the Q-T interval. Studies of the electrocardiographic effects following a single insulin shock treatment in schizophrenia have disclosed depression of the S-T segments, flattening and inversion of the T waves, prolongation of the Q-T intervals, arrhythmias such as auricular fibrillation, auricular extrasystoles, shifting pacemaker, sinoauricular heart block, P wave changes, and slurring of the QRS complexes. The most marked electrocardiographic changes were recorded usually at the point of lowest blood sugar levels and in most instances the changes disappeared with return of these levels to normal.

Bellet and his associates[1] as well as others, have emphasized that the electrocardiographic alterations following induced hypoglycemia were completely reversible within a matter of hours in all of forty patients studied. Inasmuch as the electrocardiographic changes observed with hypoglycemia show a close similarity to those resulting from anoxemia produced by inhalation of oxygen-deficient gas mixtures, shock, and conditions which greatly increase the work of the heart, permanent damage to the myocardium might conceivably result from the biochemical alterations induced by frequently repeated episodes of hypoglycemia.

Some observations suggest that lowering the blood sugar lowers the oxygen consumption of the brain and that oxidation in this organ is lowered when the supply of oxygen or dextrose is reduced. While these findings may not apply equally to the heart, the lack of available carbohydrate as well as the increased work of the heart during hypoglycemic shock of long duration, would suggest that anoxemia may be a factor in producing the cardiac changes. The S-T interval changes observed during hypoglycemic shock are similar to those encountered by Rothschild and Kissin[2] and others after experimental anoxemia in the human subject. Indeed, the anoxemia test of Levy[5] and the exercise elec-

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trocardiographic test of Master[6] depend on the observation of similar changes occurring in persons with impairment of coronary circulation. Master[3] has stated moreover, that death from hypoglycemia as well as from hemorrhage, shock, and pulmonary embolism is frequently cardiac in origin resulting from extensive subendocardial injury.

The present study, therefore, sought to determine whether or not permanent damage resulted from frequently repeated hypoglycemic shock levels induced by insulin in the treatment of schizophrenia. Previous studies by Goldman[4] in which eleven patients receiving insulin shock therapy were investigated from time to time throughout their period of treatment and at intervals for several months afterward, indicated that electrocardiographic changes observed during coma become less and less reversible as the series of repeated hypoglycemic shocks progress. Furthermore, since some of these changes were evident as long as six months after cessation of treatment in Goldman's patients, permanent damage to the myocardium must be considered as a possible outcome of this form of treatment.

MATERIAL

Electrocardiograms were taken on 209 patients before and after a series of insulin shock treatments. Of these, 156 were male subjects and 53 were female. The average number of shocks was sixty per patient. The ages varied from 15 to 45 years. Of the 209 patients, 110 were between the ages of 15 and 25 years, 82 were between 26 and 35, and 17 were between 36 and 45. All of the patients showed a normal electrocardiogram at the commencement of study. The electrocardiogram after treatment, was taken within one week after cessation of therapy.

RESULTS

In 133 subjects of the 209 studied, the electrocardiogram at the conclusion of treatment, was essentially the same as that reported initially. In the remaining 76 subjects, some deviations were noted as shown in Table I.

TABLE I. NUMBER OF CASES SHOWING CHANGES IN VARIOUS COMPONENTS OF THE ELECTROCARDIOGRAM FOLLOWING A COURSE OF INSULIN SHOCK TREATMENTS

LEAD	R (VOLTAGE)		S-T SEGMENTS		T (VOLTAGE)		
	INCREASED	DECREASED	ELEVATED	DEPRESSED	INCREASED	DECREASED	NEGATIVE
I	1	1			1	5	
II	1			1	4	5	
III	2	2			16	20	
CF_4	6	4		1	19	11	

It can be seen that relatively few changes were observed of possible significance from the electrocardiographic viewpoint. Two tracings showed depression of the S-T segment (in one lead) and in each of these, the change was within the range of normal (0.5 mm.). Five tracings showed diminished voltage of the T wave in Lead I in the posttreatment electrocardiogram but in all of these the amplitude of the wave was still within normal limits. Analysis of the alterations of the R and T waves in the fourth lead (CF_4) revealed changes in voltage in an appreciable number of subjects (Table I).

In order to determine the significance of these findings and to evaluate the possible influence of minor variations in the placement of the precordial electrode, a study of an additional 50 subjects was undertaken. In these patients, multiple precordial leads were obtained (CF_2, CF_4, and CF_5) and great care was exercised in maintaining constant electrode placement in the individual subject. All of the studies were obtained by the same observer. Comparison of the pretreatment electrocardiograms with those following the usual course of therapy in this series, disclosed no significant alterations in the respective precordial leads. It, therefore, appeared that the changes in QRS and T voltage observed in the first series, were in all probability without significance, being due to variations in technique.

DISCUSSION

It has been repeatedly shown that induced insulin shock in schizophrenia is frequently associated with electrocardiographic changes in the nature of depression of the S-T segments, flattening and inversion of the T waves, and arrhythmias. It has also been observed that these electrocardiographic alterations are transient in nature, disappearing in a matter of hours following the shock episode. Some observers, however, have noted that these changes tend to become less and less reversible as the series of repeated hypoglycemic shocks progresses. Furthermore, inasmuch as some of these abnormalities were found to be present as long as six months after cessation of treatment, the question of permanent myocardial damage from this form of treatment requires consideration.

In our analysis of the electrocardiograms taken before and after insulin shock treatment in 259 patients suffering from schizophrenia, the absence of significant electrocardiographic changes was striking. Inasmuch as the final tracing was obtained only several days following a series of sixty shock treatments, it would seem evident that myocardial damage demonstrable electrocardiographically, did not occur. Patients with normal tracings, therefore, do not appear to develop permanent electrocardiographic changes as a result of insulin shock therapy.

It is of interest that three patients not included in this series who showed initial electrocardiographic changes of myocardial damage, revealed no further alterations in their tracings after more than sixty exposures to hypoglycemic shock levels. Such results, moreover, would not appear to be of rare occurrence. Thus, the authors have observed similar negative findings in a group of patients with previous myocardial infarction in whom prolonged exercise (double Master test) repeatedly failed to produce even the transient electrocardiographic changes of myocardial anoxia.

SUMMARY

A study before and after a series of insulin shock treatments in 259 patients with schizophrenia was undertaken to determine the incidence of significant electrocardiographic alterations. It was concluded that this form of therapy is not associated with any cumulative injury to the myocardium which could be detected in the electrocardiogram.

Thanks are due Dr. Clarence H. Bellinger and Dr. Christopher F. Terrence through whose cooperation this work was made possible.

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STUDIES ON THE RAPIDITY OF COMPLETE BLOOD CIRCULATION IN MAN

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THE determination of the fastest complete circulation time of blood in man assumed importance with the introduction of the dilution method for the calculation of cardiac output by Stewart[1] in 1897. Two procedures were proposed for use in experimental animals, both based upon the collection of a single sample of peripheral arterial blood from which could be determined the relative amount of a substance (1.5 per cent sodium chloride) injected into the right or left heart. The timing of the collection of the sample (i.e., a sample of the "plateau" concentration in the case of a steady injection, or a sample representative of the mean concentration of the entire passage of a single rapid injection of the substance) was determined by a Wheatstone bridge. This was so connected to plates arranged around an exposed femoral artery that the arrival of blood of altered conductivity caused a change in the tone heard in an earphone. In the employment of such electrical timing means and the collection of only a single representative sample in most experiments, evidence of rapid recirculation was not detected. The fact that the determination of cardiac output by dilution methods was subject to errors attributable to rapid recirculation of the injected substance was noted by Henriques[2] in 1913. Using anesthetized dogs he injected 5 c.c. of sodium sulphocyanide in one second and collected repeated samples of blood every second from a cannula in a femoral artery. When the injection was made into the left ventricle or aorta, it was not until the fourth second that the dye reached the femoral artery; the peak concentration came by the fifth or sixth second and was followed by a rapid decline. By the fourteenth and fifteenth second recirculation was evidenced by a rising concentration of the dye. The quickest complete circulation time was thus 10 to 11 seconds, since, by the fourteenth second, blood with dye in it had not only returned to the right heart and gone through the lungs back to the site of injection, but had taken 4 seconds to travel out of the sampling cannula in the femoral artery as well. When the injection was made into the right auricle, the resulting time concentration curve was much more gradual. It was also noted that while the dye was almost completely cleared from the blood stream in a few seconds when injected into the left heart, it was only partially cleared before obvious recirculation was evident following injection into the right auricle. This meant it was im-

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possible by the rapid injection of a known amount of foreign substance into the right heart or venous system, to collect a single sample representative of the degree of its dilution.

Subsequent investigators (Hamilton and his co-workers,[3,4] Nylin and Celander,[5] Cyvin,[6] and others[7]) have proposed methods to overcome this difficulty. Following the rapid injection of a dye or radioactive erythrocytes into an arm or neck vein (in both of which the arterial concentration curve is even more prolonged than with right auricular injection) serial arterial samples are taken and the time concentration curve is plotted. By employing tagged erythrocytes (Nylin[5]), there can be no error due to absorbtion of a foreign substance in the lung. Similarly, it avoids any error introduced by the slower relative circulation of plasma (and hence dye) than the red blood cells, which occupy the more central axial stream of rapid flow in the smaller vessels, although it has been proved recently that this error is small.[8] By mathematical means the descending slope is extended to zero concentration and the amount of injected substance in a mean sample thus calculated: the cardiac output follows by its comparison to the amount of the substance injected.

Studies in man of the rapidity of circulation of blood through the quickest routes can also be approached through these curves. In a series of sixteen curves obtained in the course of determining the cardiac output by the dye injection method, Hamilton and his co-workers[9] determined the total circulation time and found it to range from 10.0 to 18.0 seconds, with an average of 14.7 seconds. In an earlier similar investigation a time of 13.5 seconds was found in an excited man, and 31 seconds in a quiet man.[3] Moore and his associates[10] injected phenoltetraiodophthalein into the jugular vein and reported complete circulation times of 16.4 and 17.2 seconds in two different men on the basis of arterial concentration curves.

The more direct methods of measurement employed on dogs have, in general, indicated a more rapid circulation time for the shorter circuits. After injecting dye into the jugular vein of dogs, Moore and his associates[10] took serial samples through a needle in the left ventricle. The complete circulation times with this procedure ranged from 6.8 to 20.0 seconds. Starr and Collins[11] studied both the velocity and the amount of blood which traversed the rapid circulatory paths in dogs by injecting vital red into the left auricle and taking simultaneous samples every 5 seconds from both aorta and pulmonary artery. They found that the minimal amount of blood reaching the pulmonary artery in 10 seconds was 25 per cent of the total cardiac output, in 15 seconds, 38 per cent, and that this amount varied with the blood pressure.

Further information on the rapidity of complete circulation of blood resulted from investigations of the validity of the foreign gas method for the determination of cardiac output. The rapidity of return of such a substantial quantity of blood as indicated by Starr and Collins[11] and the previously mentioned dye injection experiments was in contrast to the results of analysis of the Grollman acetylene method. In 1931 Baumann and Grollman[12] performed right heart punctures in three human beings at various intervals after they began to breathe acetylene. The sample at 13 to 20 seconds contained 5.7 per cent acetylene, at 25 to 30

seconds, 12 per cent, and at 33 to 37 seconds, 18 per cent. Starr and Collins[11] were able, in dogs, to confirm this and previous work of theirs[13] which indicated that the ability of the tissues to absorb and to give off gaseous substances in response to rapid changes in their concentration in the arterial blood resulted in slow changes in their concentration in venous blood. Thus in the same dog in which dye appeared in the pulmonary artery 5 seconds after its injection into the left auricular appendage, the carbon dioxide and oxygen concentration of the pulmonary artery blood showed no change during 15 seconds after stopping the respiration pump.

Hamilton, Spradlin, and Saam[9] demonstrated that, in a dog, acetylene introduced into one lung reappeared in the other, which was isolated except in respect to blood supply, in 8 seconds. Werkö, Berseus, and Lagerlöf[14] took pulmonary artery samples in man at various intervals after beginning the inhalation of acetylene and found no acetylene in the blood until between the tenth and fifteenth second, and then in a concentration corresponding to a content in alveolar air of 0.4 to 0.5 volumes per cent.

Thus, in dogs where direct measurements of the rapidity of recirculation have been possible, there is evidence that the fastest complete circulation can occur in 7 to 8 seconds. In human beings where the rapidity has been measured either by samples of blood from the right side of the heart after breathing acetylene, or by evidence of recirculation in arterial time-concentration curves following the rapid intravenous administration of some substance, the total circulation time has been found to vary from 10 to 31 seconds. The present investigation was undertaken to determine by more direct means the fastest complete circulation time in human beings.

METHOD

Two cardiac catheters were inserted into the right side of the heart via an arm vein. The tip of one was placed in the pulmonary artery while the tip of the other was kept in the right ventricle. The patient's own whole blood, which had been activated previously by the method of Hahn and Hevesy,[15] Nylin and Malm,[16A], and Nylin [16B] was used to fill the catheter ending in the pulmonary artery. After an interval sufficient to allow for complete mixing of any activated blood accidentally introduced into the blood stream during the course of filling the catheter, blood samples were taken through the ventricular catheter to determine the basal level of the systemic radioactive phosphorus concentration. At a given instant a rapid steady injection of activated blood was made into the pulmonary artery. This was done by applying steady oxygen pressure to the activated blood in a burette attached to the catheter. The amount (15 to 25 c.c.) and the rapidity (from 35 to 240 seconds) of the injection were noted. During the course of the injection serial samples were taken at precisely noted times from the right ventricle. At the end of the injection additional samples were taken for the determination of the total circulating red cells mass, since the exact amount of activated blood injected was known. These samples were also analyzed for oxygen content and this information coupled with the in-

dividual's oxygen consumption, which was determined immediately prior to or after the injection, to determine the cardiac output by the Fick method.

All blood samples, which were kept liquid by heparin, were then centrifuged and the hematocrit was determined. The blood corpuscles were then dried, pulverized, weighed into counting capsules, and the specific activity measured by Geiger-Müller apparatus. The activity per unit of liquid blood was calculated from the hematocrit and a specific gravity of the corpuscles of 1.08 (Hahn and Hevesy[15]).

RESULTS

The concentration of activated corpuscles in the right ventricle was plotted against the time after the beginning of the injection; the line connecting these points and its extension constituted the observed time-concentration line. A theoretical time-concentration line was also plotted based upon what the con-

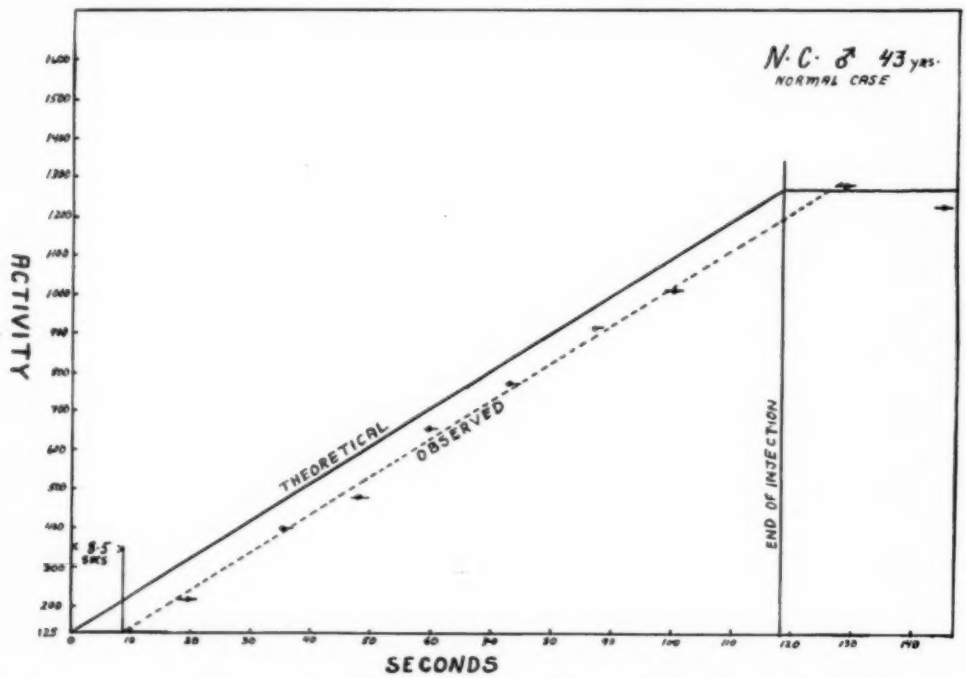

Fig. 1.—118 second continuous injection of 24 c.c. of activated blood into the main pulmonary artery with the withdrawal of seven consecutive samples of right ventricular blood during the injection. Dotted line represents the rising concentration of activated blood in the right ventricle and the extension of this line to the starting level (125) of systemic P_{32} concentration indicates that tagged red cells introduced into the pulmonary artery first returned to the right ventricle in approximately 8.5 seconds. Solid line represents theoretical time-concentration relationships calculated on basis of immediate complete mixing of the injected tagged red cells.

centration of activated blood corpuscles would have been at any instant during the injection if the mixing had been instantly complete, that is no time lag for the blood to which the activated corpuscles had been added to return to the point of sampling. By examination of the resultant graph, two observations can be

made (Fig. 1). First, the approximate time after the beginning of the injection that activated corpuscles first arrived at the sampling point in the right ventricle can be determined in each case by the beginning point of the observed concentration line. This time interval is approximate because it is almost certain that the beginning and end of this line would be curved (not straight like the extension) as increasing amounts of activated blood return and that only after some seconds would a true straight line of steadily rising concentration result. Second, by comparison of the straight portions of the two lines the time lag necessary for the concentration in the right ventricle to increase to the concentration of complete mixing can be determined. This time is simply a measurement of the mean time which is necessary for an unknown but significant (i.e. detectable) amount of activated blood to return to the point of sampling and constitutes multiple checks on the reliability of the time observed for the first arrival of activated corpuscles at the sampling point. The quickest complete circulation time must lie below both of these figures which are approximately the same. The time does not represent the mean circulation time of the entire quantity of blood, but is less, because the quickest circulating blood will have circulated many times before a single circulation of the slowest moving blood.

This experiment was performed upon three adult subjects and the results are presented in Table I. In the two normal cases, substantial complete circulation occurred in 7 to 9 seconds. In the case of rheumatic aortic stenosis (proved by autopsy) complete circulation occurred in 9.5 seconds.

TABLE I. SUMMARY OF RESULTS

PATIENT	AGE	STATUS	HEART RATE	CARDIAC OUTPUT IN LITERS PER MINUTE (FICK)	FASTEST COMPLETE CIRCULATION TIME (SECONDS)
N. C.	43	Normal	80	4.5	8.5
N. B.	40	Normal	76	3.5	7.0
L. H.	17	Aortic stenosis	72	3.4	9.5

DISCUSSION

These findings of a complete circulation time of seven to nine seconds in the shortest circuits of man differs from previous observations in human beings. It is in keeping with the previously mentioned observation of Henriques of 10 seconds for a dog and also the short time of 5 seconds obtained in an investigation of a dog by Starr and Collins.[11] This latter figure was obtained in an investigation of the rate at which changes in the gas content of the arterial blood are reflected in venous blood. When dye was injected into the pulmonary artery at the same time as the respiratory pump was stopped, a sample taken from the right heart during the following five seconds contained large amounts of dye, although the carbon dioxide content was not altered. Since this rapid complete circulation presumably entails the coronary circulation and the lungs, and since

the distances and pressures involved in that circulatory route in man and dogs differs very slightly, it seems unlikely that the time for complete circulation should differ greatly. The determinations by Henriques and Starr are direct observations. Those of Henriques involve left ventricular and aortic injections and this results in arterial time concentration curves in which there is almost complete dye clearance before apparent recirculation. It gives, as well, a measurement of the time for passage of blood from the left ventricle to the sampling needle (4 seconds to the dog's femoral artery). The method of Starr and Collins was in essence similar to the one employed in this experiment, that is, injection into the pulmonary artery and sampling from the right heart which has an error of only the short time necessary for blood to pass from the right ventricle to the sampling point in the pulmonary artery. In the present experiment the distance between the tips of the two catheters was about 6 to 7 centimeters.

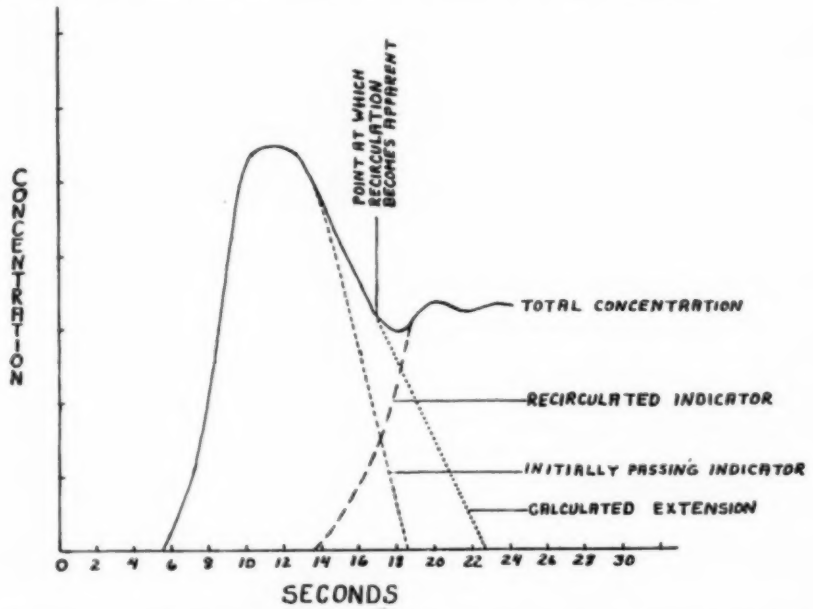

Fig. 2.—Component parts of a theoretical arterial time-concentration curve following the rapid injection of an indicator into a vein. Indicator appears first at 5.5 seconds. Recirculation begins approximately 8 seconds later at 13.5 seconds, supplements the concentration of the initially passing indicator, and contributes to the descending slope of the total concentration curve so as to: 1) obscure the point of recirculation until the eighteenth second when it becomes apparent: 2) cause incorrect extension of the curve beyond the point of apparent recirculation.

The methods previously employed in man have involved less direct procedures. The detection of acetylene in samples of blood from the right side of the heart as done by Baumann and Grollman,[12] and by Werkö and his coworkers,[14] measures at best the rate of blood which was just ready to leave the alveolar capillaries when the acetylene breathing begins, and thus measures the time for passage through only a portion of the complete circuit. The possibility of absorbtion of acetylene by the tissues may delay its appearance in the right

side of the heart, thus giving too slow a time for recirculation. The evidence of Starr and Collins[11] indicates that this is an important factor and may more than offset the too rapid circulation measurements caused by the less-than-full circuit.

Examination of arterial time-concentration curves for the point of recirculation reveals similar uncertainties. The time on the descending limb at which there is a definite deviation from the curve, or straight line if plotted on semilogarithmic paper, of falling concentration is merely the point at which the proportion of twice circulated blood in the artery is increasing as fast as, or more quickly than, the proportion of initially circulating blood is falling, thus creating the break in the total concentration curve. It is not the time at which recirculation begins, but the time at which it becomes manifest. It can be seen that the time at which recirculation becomes apparent in such a curve is delayed by itself—the error tends to hide itself (Fig. 2). The greater its amount and the earlier its occurrence, the more recirculated blood tends to contribute to the formation of the descending limb, making its descent more gradual and thus prolonging the point at which its contribution makes the time-concentration curve break its smooth descent.

On the basis of the results of this experiment, blood which previously has been around the shortest circuits can reappear in measureable quantities in blood from the femoral or radial artery by the eighth second after the first appearance of the indicator at the point of sampling, that is, 12 seconds after the first entrance of the indicator into the aorta. This confirms the work of Henriques[2] and its applicability to human beings. And since recirculation may alter the concentration curve so that its presence is not detectable until some seconds later, the calculation of cardiac output by the dilution method must be from a curve in which the mathematical extension of the descending limb is determined prior to the eighth or ninth second after the first appearance of the diluted indicator. Otherwise, recirculating blood and indicator may contribute unbeknownst to the slope of the curve at a point where it will tend to obscure itself and to produce errors in the calculated extension of the slope and thus in the cardiac output.

SUMMARY

1. During the course of a steady injection of tagged erythrocytes into the main pulmonary artery of human beings, serial samples of right ventricular blood were taken. The results indicated that detectable complete circulation occurred by the seventh to ninth second.

2. Calculations of cardiac output by the dilution method must be made from arterial time-concentration curves in which the characteristics of the descending limb can be calculated prior to the eighth or ninth second after the first appearance of the injected substance.

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ELECTROKYMOGRAPHIC STUDIES IN ANEURYSM OF THE LEFT VENTRICLE

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RECORDINGS of the motions of the heart in intact man have been of interest to cardiologists and physiologists for a considerable length of time. Following the pioneer work of Stumpf, Weber, and Weltz,[1-3] it was hoped that roentgenkymography would provide the means for detailed study of the motions of the heart chambers both in normal and abnormal hearts. Studies were made especially of left ventricular pulsations after myocardial infarction.[4-8] However, because of technical limitations and because of the relative paucity of information obtained, interest in roentgenkymography waned.

Various attempts have been made to record heart border motions with the aid of a photoelectric tube. It remained for Henny and Boone[10] to develop an electrokymograph suitable for recording heart border motion, utilizing a photoelectric cell with roentgenoscopic beams as the source of energy. They used carotid artery pulsations as reference points. Modification of this technique was made by Luisada and associates[14,15] who used heart sounds as reference points. Other investigators developed similar techniques.[11-13]

We have been interested in utilizing the electrokymograph for the study of cardiac pulsations in a series of normal individuals and for the study of left ventricular pulsations after myocardial infarction. At first we used a Cambridge Simpli-Trol* apparatus, with a pulse recorder added for simultaneous registration of the electrokymogram, heart sound tracings, and the carotid artery pulsation. Later a new piece of recording equipment became available, a direct writing three beam Technicon† and since then we have been employing this machine exclusively. We recorded the carotid artery pulse tracing, an electrocardiogram, and an electrokymogram simultaneously. Following the acquisition of a second electrokymograph, we now record two electrokymograms simultaneously, plus either the carotid artery pulsation or an electrocardiogram. In this paper we are presenting the findings in three patients with definite ventricular aneurysms and/or parodoxical pulsations. These were made in the course of an over-all study of electrokymographic patterns after myocardial infarction.

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PREVIOUS STUDIES ON VENTRICULAR ANEURYSM

According to Legg, cited by Parkinson[17] in 1938, Galeati in 1757 was the first to describe an instance of ventricular aneurysm. Hunter also described a case in 1757 but Baillie[16] was the first to describe a case in detail. Thereafter, scattered cases were reported by Breschel in 1827, Thurne in 1836 and Legg in 1883. Hall[18] reviewed 112 cases in 1903 and Sternberg[19] in 1914 reviewed all proved cases. In 1938 Parkinson[17] brought the literature up to date, adding sixteen cases of his own, thirteen of which were secondary to arteriosclerotic heart disease and myocardial infarction. Other less common causes include congenital aneurysm, perhaps better termed cardiac diverticula, trauma, necrosis of heart muscle after rheumatic myocarditis, and mycotic ventricular aneurysms secondary to acute and subacute bacterial endocarditis.

Ventricular aneurysms most often affect the left ventricle, usually near the apex on the anterior wall and, less frequently, on the posterior wall. Ventricular aneurysm may be suspected on physical examination if abnormal pulsations are noted in the precordial area apart from the apex beat when the heart sounds are faint. The roentgenographic criteria have been summarized by Schwedel[20] and include: 1. localized bulge; 2. pericardial bulge; 3. increased density due to a thrombus in the aneurysm; 4. calcification in the aneurysm; 5. incisura between normal and abnormal portions of the ventricle; and 6. paradoxical or otherwise abnormal pulsation on roentgenoscopy.

Most authors feel that there is no characteristic electrocardiographic pattern associated with ventricular aneurysm. Rosenberg and Messinger[21] have recently summarized the literature and presented their own observation on eight cases of ventricular aneurysms. They stress the presence of elevated ST segments in the chest leads from the left side of the precordium which persist long after the acute phase of myocardial infarction. Ford and Levine[22] have recently presented the data on their ten cases and they agree that ventricular aneurysm is frequently associated with electrocardiographic appearance usually interpreted as evidence of acute myocardial infarction, with persistence of this pattern over a protracted period. On the other hand Goldberger[23] feels that QRS complexes directed upwards in Lead aV_R are found in ventricular aneurysm and that the absence of this pattern argues strongly against the diagnosis of ventricular aneurysm.

Schlichter and Hellerstein[24] in a study of 102 proved cases of ventricular aneurysm suggested that inadequate bed rest at the time of the acute infarction led to localized bulges in 70 per cent of their cases. Sutton and Davis[28] showed, experimentally, that animals forced to work soon after coronary artery occlusion developed ventricular aneurysms, whereas the hearts of animals spared such effort healed without the development of ventricular aneurysms.

Luisada[25,26] has published an article on electrokymograms in myocardial infarction using heart sound recordings as reference points. Stauffer and Jorgens[27] have published similar work. As far as we know there have been no published instances where electrokymograms of the intact left ventricular area and the infarcted or aneurysmal area have been recorded simultaneously without resorting to reference points.

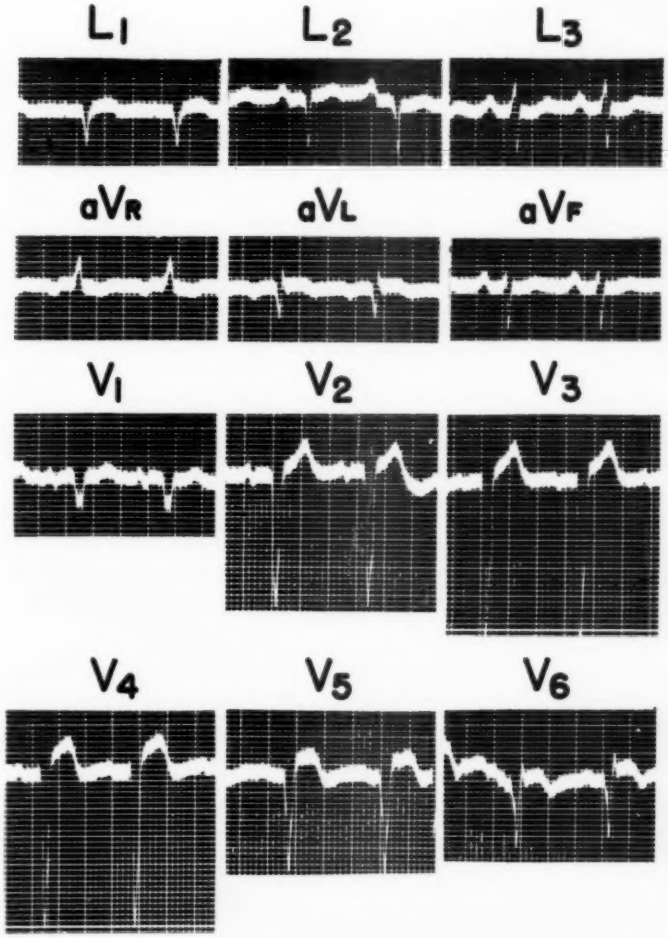

Fig. 1.—Electrocardiogram of the first patient. Myocardial infarction occurred three years before but no change has been noted in the tracings since then. Elevation of the S-T segment can be seen in Leads aV_L, V_3, V_5, V_6 and standard Lead I.

TECHNIQUE AND METHODS

This particular phase of our work has been done with the Technicon Tri-beam direct writing recording apparatus as a direct writing recorder allows for immediate visualization of the curves and permits immediate repetition of unsatisfactory tracings. Three variables can be recorded at the same time. We usually employ two electrokymograms and either the carotid pulse tracing or the electrocardiogram, but can use the phonocardiogram instead of one of the others. Tracings with this machine at least equal those obtained with other apparatus currently employed. The frequency response of the Technicon is flat to 55 cycles per second. Each channel possesses a separate balancing mechanism to eliminate 60 cycle interference and another for critical damping of each stylus separately.

The electrokymographic equipment consists of a standard phototube housing containing a photoelectric cell mounted on the back of a roentgenoscopic screen and connected in turn to a power box containing a filter which removes ripples on the curves produced by roentgen ray beams. A fully rectified roentgenoscope was used. The carotid pulse pick-up unit consists of a microphonic transmission set at relatively low frequency. The current of the microphone pick-up device was fed into one channel of the recording apparatus. It was placed directly over the pulsating vessel so that only pressure tracings were obtained.

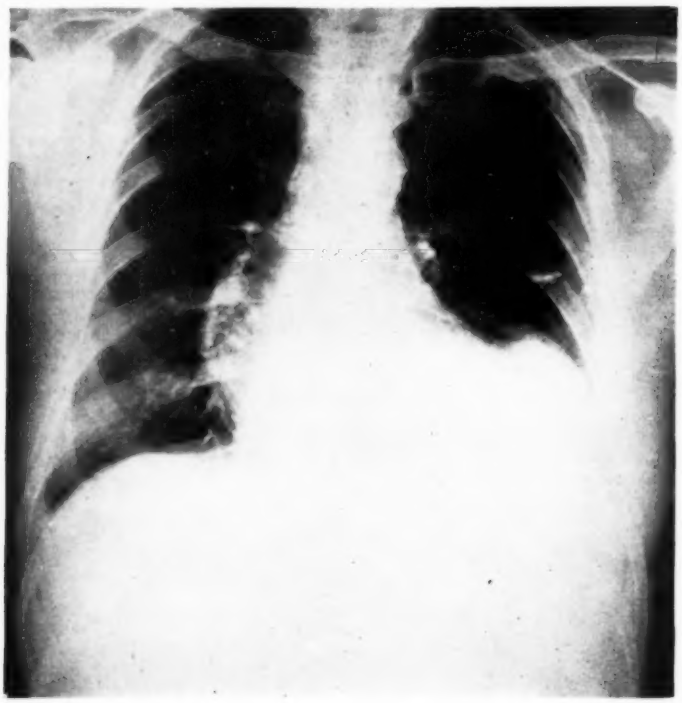

Fig. 2.—Chest roentgenogram of the first patient. A localized aneurysmal bulge is visible on the upper portion of the left ventricular contour.

Fig. 3.—Electrokymograms of the first patient. The upper curve on all three strips represents the carotid artery pulse tracing. The middle curve represents the electrokymograms of the aneurysmal area of the left ventricle and the normally pulsating left ventricular portion. The lower curve is Lead I of the electrocardiogram. These curves were recorded on the Technicon. Points 1 and 5 represent the onset of the ejection phase on the carotid pulse and Points 3 and 7 represent closure of the aortic valve and the onset of the isometric relaxation phase of the left ventricle. Point 2 represents onset of ventricular ejection on the normal portion of the left ventricle. The downstroke is recorded as the ventricle contracts with inward movement of the ventricular contour. In contrast, it can be seen that at Point 6 systolic paradoxical expansion occurs on the contour of the aneurysmal area. Point 4 represents onset of the left ventricular isometric relaxation phase. Shortly after this point, ventricular filling with upward expansion of the curve is noted. In contrast, at the corresponding Point 8, a downward curve, or early diastolic collapse of the aneurysmal area is noted, at a moment when the normal left ventricular contour is expanding. Clearly the pulsations of the aneurysmal area are reversed, are paradoxical.

Please note the shift of the ventrical line indicating simultaneous events on the three curves. This is due to a 0.03 second delay in the registration of events on the carotid pulse and represents the time required for pulse wave to travel from the heart to the carotid vessel in the neck. The delay is thus not merely mechanical in origin.

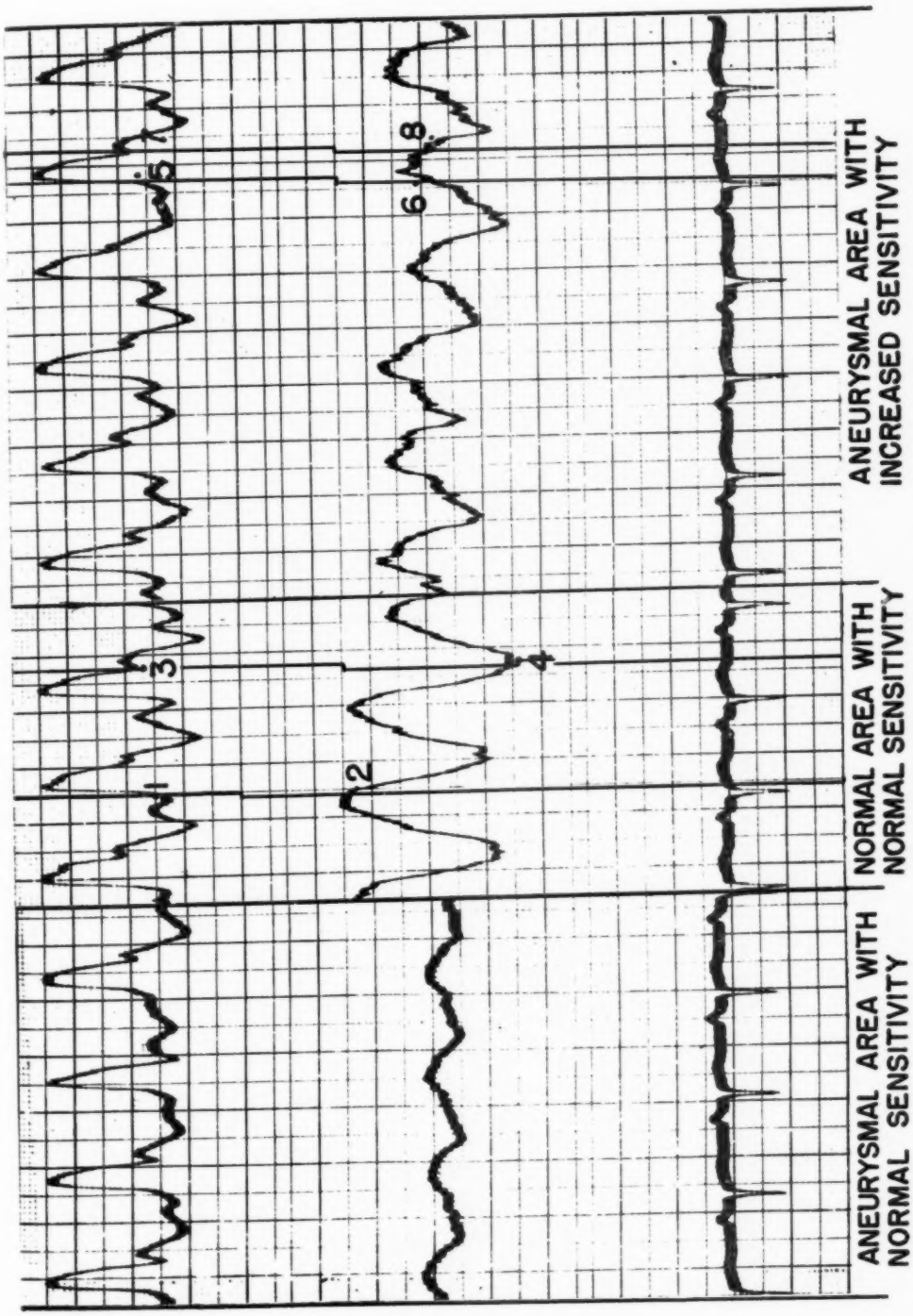

Fig. 3. Legend on opposite page.

The electrokymographic curves were all taken with the patient in the sitting position. The photoelectric cell was situated between the patient and the roentgenoscopic screen. The operating factors of the fluoroscope were 4 to 5 ma., usually at 70 to 74 kv. The paper speed was 25 mm. per second since we found that sharper definition of the curve end points were obtained at this speed rather than with faster speeds where sharp end points necessary for accurate interpretations of the tracings were lost. Tracings were taken in the posteroanterior view and in varying degrees of right and left anterior obliquity.

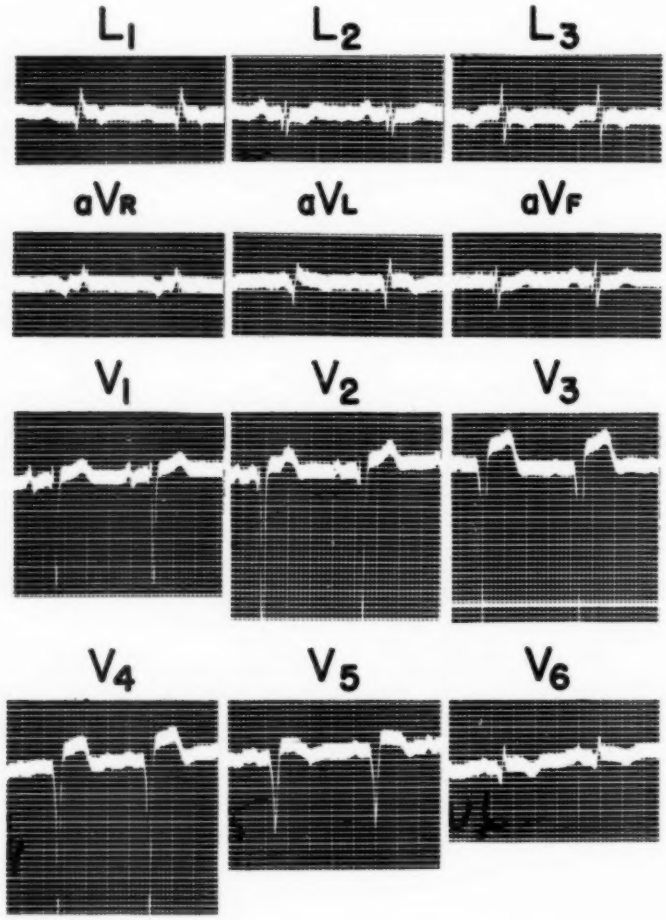

Fig. 4.—Electrocardiogram of the second patient. Myocardial infarction occurred two years ago, (1947) but no change has been noted in the tracings since then. Elevation of the S-T segment in Leads aV_L, V_3, V_4, V_5, and V_6 is apparent.

RESULTS

Three patients were studied. Their clinical histories and findings are summarized here.

CASE 1.—The first patient was a 58-year-old white man with known hypertension for many years. Four years ago (1945) his blood pressure was 240/140 mm. Hg. One year later he developed dyspnea, swelling of the lower extremities, and angina pectoris. The electrocardiograms at that time and at the time of writing show significant Q waves and S-T elevation in the precordial leads, as shown in Fig. 1. Roentgenoscopy showed a localized ventricular bulging of the lower two-thirds of the left ventricular contour in posteroanterior position with paradoxical pulsation. Roentgenograms showed the bulge (Fig. 2).

Electrokymographic studies of the "normal" left ventricular contour taken simultaneously with the carotid pulse tracing and Lead II of the electrocardiogram are shown in Fig. 3. It will be noted that the systolic downstroke in the normal portion of the left ventricle corresponds to the upward ejection phase of the carotid artery pulse tracing. The diastolic rise in the normal left ventricular curve begins shortly after the carotid incisura. Contrast this with the curve in the aneurysmal area (Fig. 3). Here there is a rise in the ventricular curve during early systole, in the same direction as the carotid pulse tracing. The ventricular curve starts to fall sharply only after the carotid incisura although there is a lesser fall in late systole. Clearly the direction of pulsation in aneurysmal bulge is opposite in direction to the normal left ventricular segment.

CASE 2.—The second patient was a 49-year-old Negro man who gave a history of prolonged chest pain with left arm radiation two years ago (1947) for which he was hospitalized for six weeks. The electrocardiogram (Fig. 4) shows deep Q waves and elevated S-T segments in the precordial unipolar limb leads. Tracings at present show no significant change. On fluoroscopy it was noted that the lower one-half of the left ventricular curve in the posteroanterior position pulsated outward during systole; the upper half was relatively normal. The roentgenogram is shown in Fig. 5.

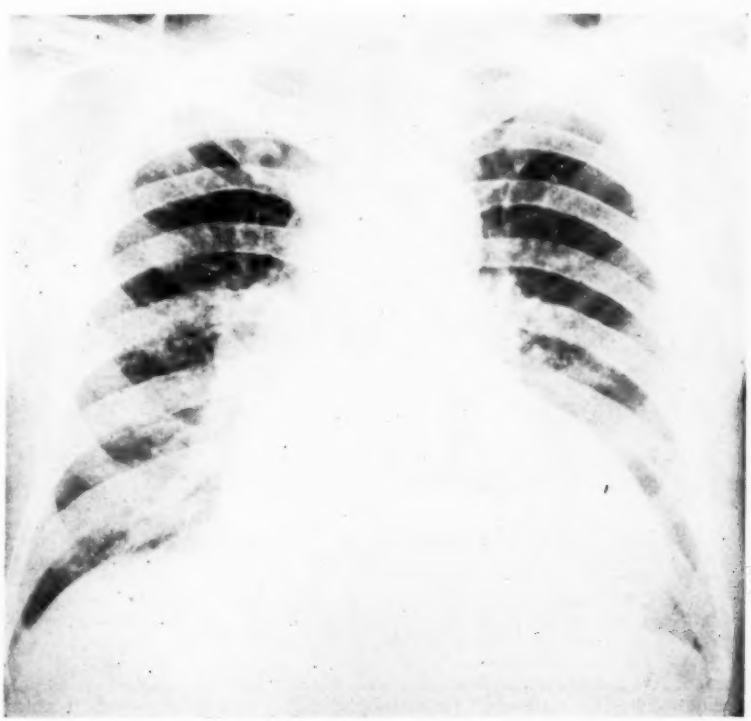

Fig. 5.—Chest roentgenogram of the second patient. Marked left ventricular enlargement can be noted without a definite aneurysmal area.

The electrokymogram, (Fig. 6) indicates that the ventricular curve of the upper normal portion descends during the rise in the ejection phase on the carotid tracing. The curve of the abnormal lower left ventricle is upward in systole, in the same direction as the carotid artery pulsation. The movements in late systole are also oppositely directed to the normal.

CASE 3.—The third patient was a 56-year-old white man with an authentic history of myocardial infarction three years ago (1946). The electrocardiograms are those of an anterolateral infarction but there is no S-T segment elevation in the precordial leads (Fig. 7). Neither is the

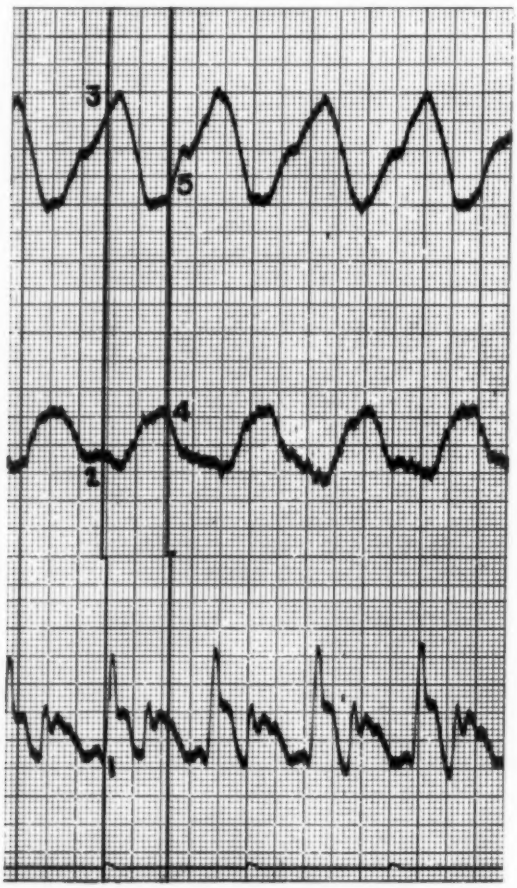

Fig. 6.—Electrokymogram of the second patient. The uppermost curve represents the electrokymogram of the normal upper half of the left ventricular contour. The middle curve shows pulsations of the lower one-half of the abnormally pulsating left ventricular contour. The lower curve is a combined curve showing the common carotid artery pulse with venous pulsations superimposed. The three curves have been recorded simultaneously. At Point 1, the onset of the ejection phase on the carotid pulse, there is first an upward, then a downward motion of the normal part of the left ventricle at Point 3. This upward movement is normally seen most frequently in early ventricular ejection and is probably torsional in origin. On the middle curve, shortly after Point 2, marked systolic expansion is noted. At Point 5, normal diastolic filling of the left ventricle occurs, while a curve of the abnormal area at Point 4 shows abnormal diastolic collapse. Clearly the pulsations of the lower ventricular border are paradoxical. Again please note the shift of the vertical line due to the 0.03 second delay in the carotid pulse tracing.

QRS complex directed upward in the right arm lead. Roentgenoscopy indicated a large localized left ventricular bulge of the left ventricle with paradoxical pulsation of the abnormal portion. The roentgenogram is shown in Fig. 8.

Electrokymograms, taken simultaneously, of the normal and aneurysmal areas (Fig. 9) show an upward curve during early systole over the abnormal lower three-fifths of the left ventricle. The pulsation of the upper "normal" two-fifths of the left ventricular was downward in early systole as was to be expected but continued downward after the carotid incisura, that is in early diastole. The normal left ventricular pattern here is thus only relatively normal, also showing an abnormal type of pulsation in that early diastolic collapse occurred, instead of rapid early diastolic filling.

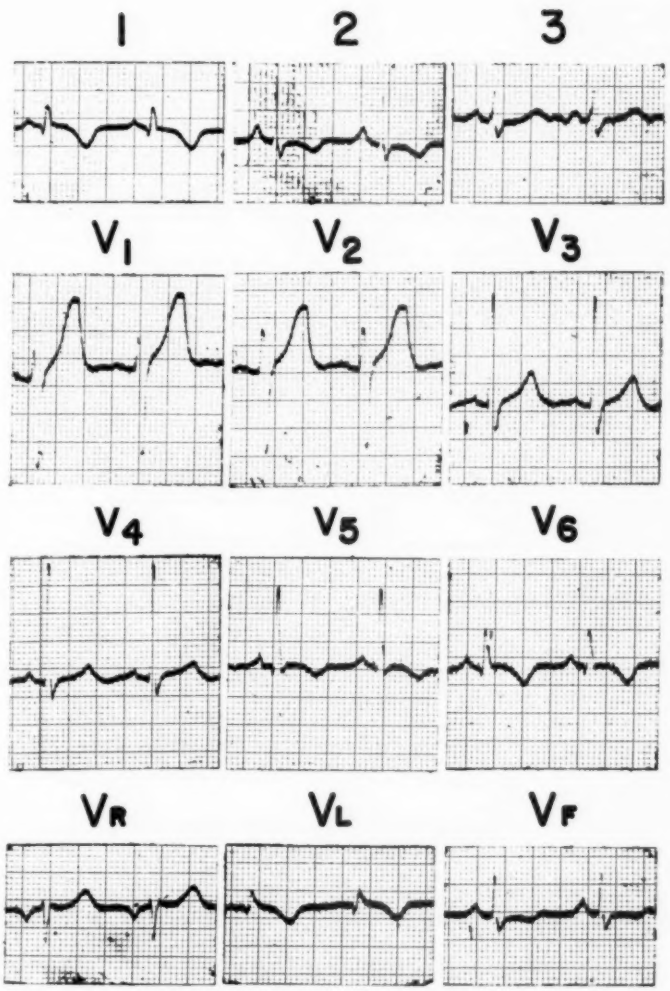

Fig. 7.—Electrocardiogram of the third patient. Abnormal S-T elevations are not seen in this case, but the changes in V_L, V_5, and V_6 are in favor of anterolateral myocardial infarction.

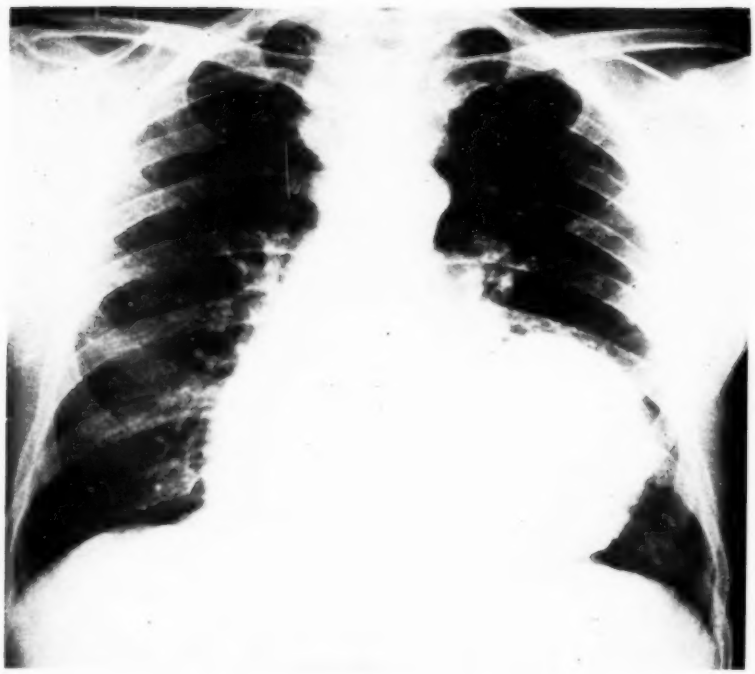

Fig. 8.—Chest roentgenogram of the third patient. The massive aneurysmal bulge occupying almost the entire left ventricular contour is seen.

DISCUSSION

In their roentgenkymographic studies after myocardial infarction, Sussman, Dack, and Master[7] noted several types of abnormalities: 1. diminished or absent pulsation in a localized segment of the left ventricle; 2. systolic expansion, partial or total; and 3. marked diastolic splintering, manifested by irregularities of the curve in diastole.

Luisada and Fleischner[25,26] suggest that nine patterns of ventricular pulsation are abnormal, but only two are pathognomonic. These include the disappearance of, or localized reduction in, the amplitude of the wave of the left ventricular contour and, secondly, paradoxical pulsation, termed "dynamic aneurysm."

Each of our cases showed the phenomenon of paradoxical pulsation with systolic expansion and early diastolic collapse. Diminished localized pulsation, requiring increase in amplification, was not demonstrated.

In our experience paradoxical pulsations early or late in systole, and early diastolic collapse are pathognomonic of localized damage. The other abnormalities noted by Luisada could be duplicated by oblique shifting of the photoelectric tube slit or other incorrect placing of the photoelectric cell. Further observations are necessary to establish these criteria.

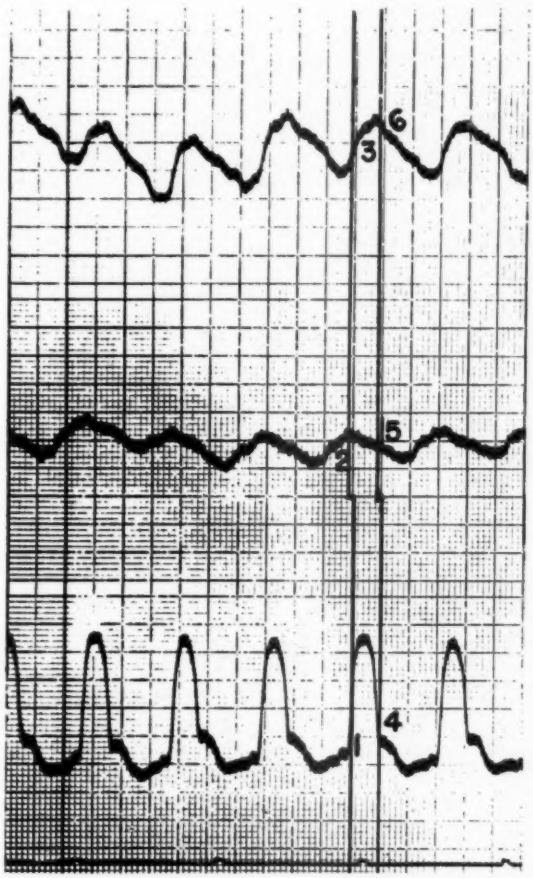

Fig. 9.—Electrokymogram of the third patient. The uppermost curve is from the aneurysmal lower three-fifths of the left ventricular contour. The middle curve is from the upper relatively normal two-fifths of the left ventricular contour. The lowermost curve is the carotid pulse tracing. At Point 1, onset of the systolic expansion of the carotid curve is seen, but at the corresponding Point 3, marked systolic expansion instead of systolic inward movement is noted. At Point 2, a small downward movement is noted. At Point 4, the moment of closure of the aortic valve and onset of left ventricular isometric relaxation phase, both curves at Points 5 and 6 show downward movements, or diastolic collapse, instead of the normally occurring diastolic expansion, as would be shown by upward movements at Points 5 and 6. Paradoxical pulsations are thus present on both ventricular curves. Again please note the shift of the vertical lines due to the 0.03 second delay in the carotid pulse tracing.

At present we are limited in the application of the electrokymogram in the discovery of abnormal left ventricular pulsations by the necessity of first finding such areas on fluoroscopy. However, we are investigating the ventricular pulsations following myocardial infarction irrespective of roentgenoscopic impressions and hope to be able to report on a large series soon. To date we have found one instance where abnormal paradoxical pulsations were recorded with the electrokymogram in a case where paradoxical pulsation was sought but not found on fluoroscopy.

SUMMARY

Three cases showing paradoxical pulsation of the left ventricular contour on fluoroscopy and electrokymography have been presented. In two of these a definite ventricular aneurysm was apparent on x-ray examination. The electrokymographic criterion for a localized area of ventricular damage is the demonstration of systolic expansion or diastolic collapse.

We are indebted to Dr. Arthur C. DeGraff, Senior Consultant to the Medical Service, Veterans Administration Hospital, Bronx, N. Y., for his aid and encouragement which made this work possible. We are also greatly indebted to the personnel of the Technicon Co., for the use of their machine, materials, service, and technical advice.

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Clinical Reports

TRICUSPID STENOSIS WITH SURVIVAL TO THE AGE OF 61 YEARS

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IT IS very unusual for a person with severe stenosis of the mitral, aortic, and tricuspid valves to reach the seventh decade. We are herewith recording such a case.

CASE REPORT

History: The patient (M. S.) was a white woman aged 52 years at the time of her admission to the Massachusetts General Hospital in December, 1940.

In 1910, at the age of 22 years, while in nursing training at the Massachusetts General Hospital the patient had her first attack of rheumatic fever with recurrence in 1912. Following periods of rest each time the patient was able to complete her course but had a third attack of rheumatic fever in 1915 at which time her heart was found to be abnormal. There was no evidence of cardiac failure until 1938.

In December, 1940, a diagnosis of rheumatic heart disease with mitral stenosis, mitral insufficiency, and aortic insufficiency was made. There was cardiac enlargement with atrial fibrillation and questionably active rheumatic fever at this time.

In 1941, the patient was readmitted to the hospital with the tentative diagnosis of subacute bacterial endocarditis. The physical examination was unchanged. Subsequent blood cultures taken during the period of hospitalization did not confirm this diagnosis.

In 1943, pleural effusion on the right side and ascites developed. Thoracentesis was necessary on two occasions.

At the time of examination in November, 1945, the patient had had nine previous abdominal paracenteses. The rest of the past medical history was noncontributory except for an appendectomy in 1938 and the data presented above.

Physical Examination: In November, 1945, physical examination revealed moderate emaciation and dyspnea. There was a slightly icteric and cyanotic color to the skin and mucous membranes. The head and neck were normal except for a constant and marked, deep systolic jugular pulse. Percussion of the thorax revealed marked cardiac enlargement both to right and to left. There was a systolic thrill in the aortic area. Auscultation of the heart revealed both rough systolic and rumbling mid-diastolic murmurs at the apex. At the aortic area there were also systolic and diastolic murmurs; the latter was early in time and blowing in type. There was an additional localized mid-diastolic murmur at the tricuspid area. The examination of the lungs revealed moist râles at the right base. The abdomen was protuberant and a fluid wave was demonstrated. The liver was palpable three fingerbreadths below the right costal margin. The spleen was not palpated. There was a moderate degree of edema of the sacrum and legs.

Laboratory Tests: The examination of the urine revealed a specific gravity of 1.010; there was a trace of albumin but no sugar was found; there were 10 to 15 leucocytes per high power field. The blood counts revealed normal levels for both leucocytes and erythrocytes and no abnormal cells in the differential blood smear. The nonprotein nitrogen concentration was 22 mg. per 100

c.c. of whole blood. The serum protein measured 6.1 Gm. per cent with reversed albumin-globulin ratio (0.9), the albumin 2.9 Gm. with the globulin 3.2 Gm. per 100 c.c. of whole blood. The Kahn test of the blood was negative. The electrocardiogram revealed atrial fibrillation (Fig. 1). The S-T segments were depressed in Leads I, II and CF_5. The T waves were diphasic in Lead I, isoelectric in Lead II, and inverted in Lead III. An x-ray film of the thorax (Fig. 2) revealed marked cardiac enlargement to both left and right. The enlargement was most marked in the regions of the right and left atria. The lung fields were relatively clear with no fluid present in the costophrenic angles.

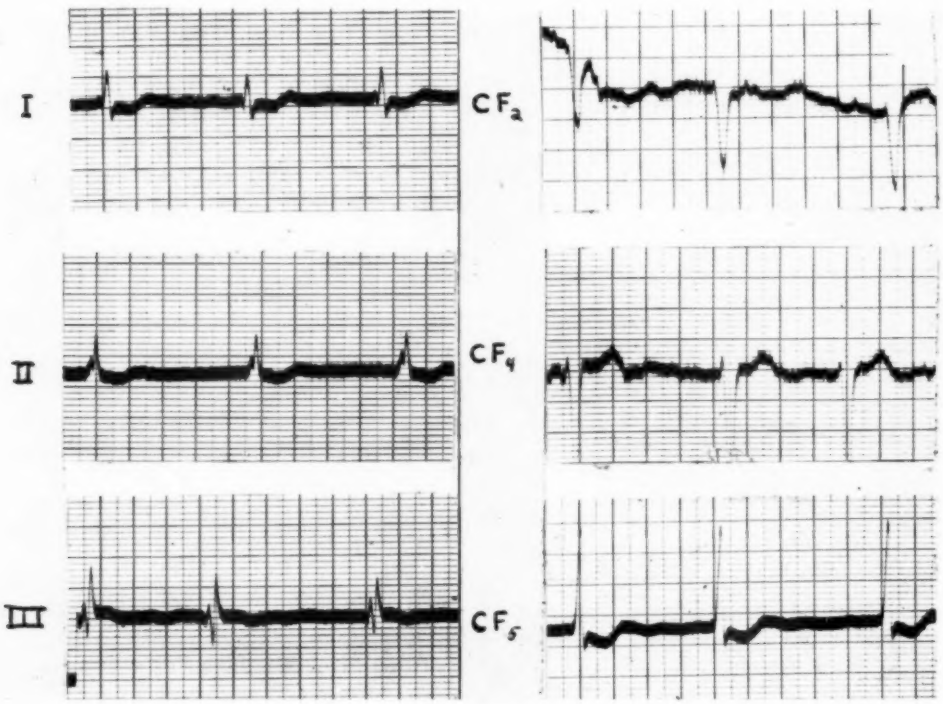

Fig. 1.—(M. S.) Electrocardiogram showing atrial fibrillation, with only slight ventricular arrhythmia, in a case of stenosis of mitral, aortic, and tricuspid valves. May 27, 1947.

The clinical diagnosis at this time (November, 1945) was rheumatic heart disease with mitral, aortic, and tricuspid stenosis. The patient was placed on a low-sodium neutral ash (Schemm) diet. The maintenance dosage of digitoxin 0.1 mg. daily was continued. In addition the following medications were administered: enteric sealed ammonium chloride tablets 5 Gm. (75 grains) daily, brewer's yeast 12 tablets daily, vitamin B complex 2 capsules daily. Mercuhydrin was injected in the dosage of 1 c.c. at intervals of four to five days. An abdominal paracentesis was performed. On this regime there was weight loss from 147 pounds to 104 pounds. The patient was discharged from the Massachusetts General Hospital on Nov. 11, 1945.

From this time until her death on Feb. 8, 1949, her time was spent in Boston, Mass., Maine, and St. Petersburg, Fla. Her clinical course was checked at frequent intervals. This period was characterized by recurrent ascites and ankle edema. Abdominal paracentesis was necessary on the average of once every two months. Dyspnea during this period of time was never prominent except just before abdominal paracentesis when there was marked abdominal distention. While the patient was in Florida, abdominal paracenteses were done in January, 1946, March, 1946, January, 1947, and December, 1947. When the patient was re-examined on Dec. 2, 1947, it was reported

that during the period from April, 1947, to October, 1947, no abdominal paracentesis was necessary. The physical examination was not changed from that previously recorded. An increase in strength had been observed. Paracentesis was again performed in February, 1948.

The patient was observed again in St. Petersburg, Fla., on Dec. 13, 1948. On this date she was admitted to St. Anthony's Hospital in St. Petersburg, Fla. The chief complaints at this time were nausea, vomiting, abdominal pain, and weakness. The history revealed that while the patient was in Maine a rubber catheter had been inserted in the peritoneal cavity for the purpose of drainage of ascitic fluid. Since the insertion of the catheter the patient had drained approximately 1,500 c.c. of ascitic fluid every four or five days. Weakness and listlessness were present.

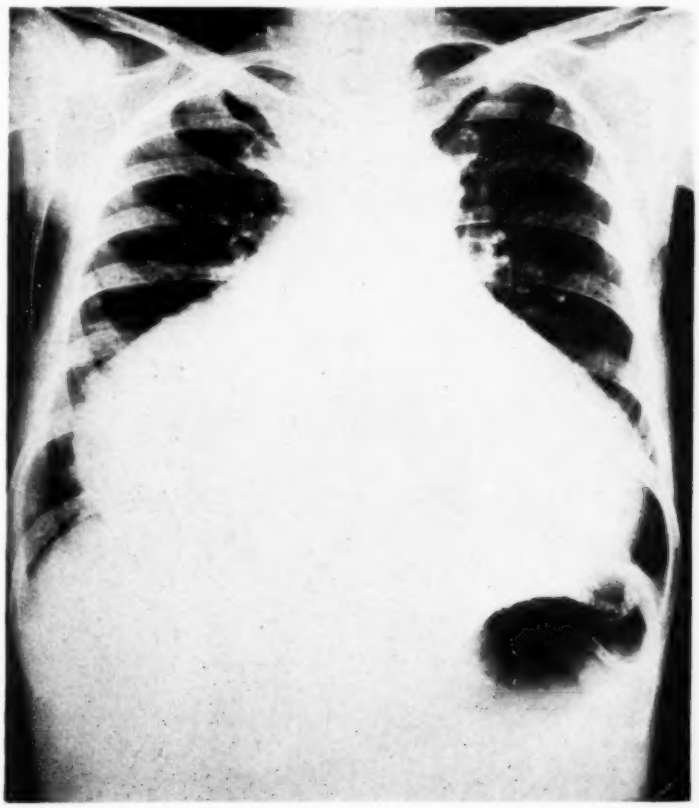

Fig. 2.—(M. S.) Roentgenogram of the thorax revealing marked cardiac enlargement.

The results of physical examination revealed a chronically ill white woman, aged sixty years. The temperature was 98.6° F. The pulse rate was 72 beats per minute. The blood pressure measured 150 mm. Hg systolic and 80 mm. Hg diastolic. The skin had a characteristic color, representing a combination of cyanosis and icterus, classically described as occurring in patients with tricuspid stenosis. A deep, systolic, jugular vein pulsation was observed. The examination of the heart revealed mitral and aortic diastolic and systolic murmurs with a systolic thrill in the aortic valve area. A diastolic murmur was also heard below the xiphoid cartilage in the tricuspid valve area. Auscultation of the lungs revealed no râles. The abdomen was only moderately distended, but tenderness and muscle resistance were observed in the lower abdomen. The peritoneal catheter, which now was obstructed, was removed. There was marked ankle edema.

The results of studies of the urine were unchanged. The concentration of hemoglobin was 10.55 Gm. per 100 c.c. of blood. The erythrocytes numbered 4.1 million and the leucocytes 15,600 per c. mm. of blood. The percentage of the various types of leucocytes were as follows: segmented polymorphonuclears, 84 per cent and lymphocytes, 16 per cent.

The presence of generalized peritonitis was suspected and the administration of penicillin (50,000 units every third hour) and of streptomycin (250 mg. every third hour) was started. On the third day after admission the rectal temperature rose to 101° F. but with this exception the patient remained afebrile. There was improvement in the nausea and the vomiting subsided. The abdominal tenderness and muscle rigidity disappeared, but moderate abdominal distention continued. The ascites was adequately controlled with ammonium chloride, Mercuhydrin, and a salt-free diet so that further abdominal paracentesis was not necessary. Ankle edema was present and edema of the sacrum, hands, and arms became increasingly prominent. Progressive listlessness developed with a terminal comatose state. Death occurred on Feb. 8, 1949, sixty days after the final hospital admission.

Fig. 3.—(M. S.) Tricuspid valve revealing advanced stenosis viewed from above.

Observations at Necropsy: The following pathological diagnosis was made: rheumatic heart disease with mitral, aortic, and tricuspid stenosis, generalized suppurative peritonitis, bilateral hydrothorax, chronic passive congestion of the liver, and cardiac cirrhosis of the liver.

The examination of the thorax revealed about 500 c.c. of clear straw-colored fluid in each pleural cavity. The lungs weighed 550 grams together. In the lower lobes of both lungs there were areas of atelectasis. The bronchi and pulmonary vessels were normal. The cut surfaces of the lower lobes of the lungs revealed increased granularity with decreased crepitation.

In the pericardial cavity there were 150 c.c. of clear fluid. The pericardium was normal and free of adhesions. The heart was much enlarged in volume but relatively not so much in weight which was 575 grams. The greatest transverse diameter of the heart measured 24 cm. (normal for her size about 10.5 cm.). In the unopened state there was extreme dilatation of both atria. The inferior vena cava, which was markedly enlarged, measured 5 cm. in diameter. The greatest

enlargement, which was to the right, was due to the marked dilatation of the right atrium. Antemortem mural thrombi were present in the right atrium. The interatrial septum was intact with a closed foramen ovale.

Fig. 4.—(M. S.) Mitral valve revealing advanced stenosis. The left atrium has been opened.

Fig. 5.—(M. S.) Aortic valve revealing advanced calcareous aortic stenosis.

When the heart was opened the points of chief interest lay in the tricuspid, aortic, and mitral valves, all of which showed stenosis. The tricuspid valve, viewed from the right atrium (Fig. 3) revealed marked stenosis. This valve was greatly deformed with thickening of the valve leaflets

and contraction of the tricuspid ring; the atrioventricular orifice was ovoid in shape. It formed a fixed aperture in the valvular diaphragm and it measured 1.8 cm. in diameter. There were several small gray nodules and one large fibrous mass attached to the free margin of the tricuspid valve. The chordae tendineae were thickened. The pulmonary valve contained three cusps and was normal. The left atrium was markedly dilated. The mitral valve viewed from the left atrium (Fig. 4) revealed advanced stenosis with a narrow fish mouth opening which measured 1.8 cm. in length. The chordae tendineae were thickened. The aortic valve was also thickened with calcification of all three cusps with resulting fish-mouth stenosis (Fig. 5). The wall of the right ventricle measured 1.0 cm. in thickness and that of the left ventricle 2.5 cm. The coronary vessels were normal.

In the peritoneal cavity there were about two liters of thick purulent fluid. Fibrinous adhesions and multiple abscesses matted loops of bowel together in the right side of the abdomen and in the pelvis. The liver, which was atrophic, weighed 500 grams. The surface was dark brown in color. The cut surface revealed fibrosis with irregular brown lobules. The serosal surface of the gall bladder was covered with fibrous adhesions. The biliary ducts were patent. The spleen weighed 175 grams; it appeared normal. The kidneys weighed 325 grams together. Their capsules stripped easily and revealed finely granular, red surfaces. The cut surfaces of both kidneys revealed distinct medullae and cortices. The calices, pelvices, and ureters were normal. The pancreas, uterus, and ovaries were normal except for adhesions and abscesses in the pelvis.

Microscopic study revealed the following findings. In the lungs there was marked peribronchial fibrosis with infiltration of lymphocytes and plasma cells. Areas of atelectasis were present. The alveolar septae were thickened and in some instances fused, while in other areas small hyalinized tufts projected into the alveolar spaces. Relatively few pigmented macrophages were observed. The smaller pulmonary arteries revealed endothelial thickening.

In the sections of the myocardium there was marked scarring, predominately in the perivascular areas, the papillary muscles, and in the subendocardium. Groups of fibroblasts with a linear or fusiform arrangement were present and lymphocytes were present in the fibrotic areas. Many of the remaining muscle fibers revealed swelling, vacuolization, and loss of striation. Pyknotic nuclei were numerous.

The epicardium was infiltrated with a few lymphocytes. The coronary arteries revealed minimal narrowing of their lumina due to intimal proliferation.

In the liver there were fibrosis, atrophy, and minimal regeneration consistent with the histologic appearance of cirrhosis. Atrophy of the hepatic cells about the central vein was observed in some lobules together with necrosis in other lobules. Fibrosis was present in the periportal areas, together with newly formed bile ducts. Regenerating hepatic cells were present at the periphery of some lobules. The capsular surface of the liver was covered with fibrinous adhesions. The spleen showed chronic passive congestion.

In the kidneys the glomeruli were intact. There were albuminous casts in the tubules with swelling of the epithelial cells in the convoluted tubules. Capillary enlargement was present.

DISCUSSION

This patient presented the classical clinical features of tricuspid stenosis, which included chronic deep systolic jugular pulsation, mitral and aortic diastolic and systolic murmurs with aortic systolic thrill, and a diastolic murmur in the tricuspid valve area. There was marked and recurrent ascites during a period of six years before death. It was estimated that approximately 35 to 40 abdominal paracenteses were performed in this period of time. The roentgenogram of the chest revealed marked cardiac enlargement with tremendous increase in size of the right atrium. Nevertheless, for six years after the development of clinical evidence of tricuspid stenosis the patient was able to adjust her life to her physical disabilities. Death at the age of 61 years occurred as a result of generalized peritonitis and not of heart failure.

The clinical diagnosis in this case of tricuspid stenosis was established four years prior to death, and confirmed at autopsy. The survival of this patient into her sixty-second year is noteworthy. In the series of cases recorded by Cooke and White[2] the average age at death was 23 years. The longest survival time in that series was 51 years. Out of eight patients who came to autopsy in the series, five patients died apparently of the disease itself with extensive congestion, two died of cerebrovascular accidents, and one died suddenly, cause unknown. In the series of 32 patients with tricuspid stenosis recorded by Smith and Levine[3] the average age at death was 34.3 years; there were only 11 patients with marked tricuspid stenosis; their average survival age was 32.5 years with the greatest age at the time of death 51 years. The oldest patient at death that we can find recorded was 69 years.[1]

An interesting feature in the evolution of this case was the apparent lateness of the first rheumatic infection. Doubtless the recurrent and long continued rheumatic process—even into middle age and later—accounted for the slow development of the classical evidence of the tricuspid stenosis. She might well have lived to 70 had not peritonitis supervened. The hazard of the method of treating obstinate ascites by the installation of a drainage tube is well illustrated in this case.

The pathological features of this case revealed rheumatic valvular endocarditis, with involvement of the mitral, aortic, and tricuspid valves. As stated by many authors tricuspid valve disease rarely occurs without involvement of other valves. The degree of stenosis in this instance was advanced in all three valves involved. The mitral and aortic lesions were typical of rheumatic endocarditis while the tricuspid stenosis was peculiarly concentric in character, leaving a small ovoid communication between the right atrium and the right ventricle. Atrophy of the liver was marked. This was apparently secondary to long standing chronic passive congestion. Minimal regeneration was observed so that the case fulfilled the requirements of cardiac cirrhosis.

SUMMARY

We have presented herewith the record of a woman who survived to the age of 61 years and 8 months despite the presence of advanced stenosis of tricuspid, mitral, and aortic valves with marked enlargement of the heart. Her death was due not to heart failure or other cardiac complications but to peritonitis resulting from the presence of an indwelling catheter inserted to facilitate the drainage of her troublesome ascites. The longest survival with marked tricuspid stenosis that we have found previously recorded was 69 years.

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CONGENITAL ANEURYSM OF THE MEMBRANOUS INTERVENTRICULAR SEPTUM WITH UNIQUE ANOMALY OF THE PULMONARY VESSELS

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CONGENITAL aneurysm of the membranous portion of the ventricular septum is a rare anomaly. Abbott,[1] in her analysis of one thousand cases of congenital heart disease, included seven of this type as the primary lesion, and nine complicating other defects. In a review of the English literature since 1900 we have found reports of nine cases.[2-9] In 1938, Lev and Saphir[7] described aneurysm of the membranous septum in two Mongolian idiots. They reviewed the world literature up to that date and found about seventy reported cases. They included an excellent review of the etiology and greatly clarified the embryological development of this lesion.

The following report of congenital aneurysm of the membranous septum is unusual because of an associated aortic insufficiency, cor pulmonale, and unique pulmonary vascular lesions.

CASE REPORT

M. O., a 39-year-old Negro woman, was admitted to Charity Hospital for the first time on Feb. 12, 1946, with the chief complaint of shortness of breath. For two months she had noted dyspnea on exertion and orthopnea. She also complained of substernal pain, intensified by walking. Pedal edema had been noted two weeks prior to admission and for one week a productive cough had been present. There was no history of syphilis or rheumatic fever.

Physical examination revealed a well-developed, well-nourished Negro woman who was markedly dyspneic. The blood pressure was 200/70 mm. of mercury. The pulse was of the Corrigan type, rate 96, rhythm regular; the trachea was in the midline. The neck veins were distended. There were crepitant râles at the left base. The apex beat was forceful and diffuse in the sixth intercostal space at the anterior axillary line. There was a loud, blowing, systolic murmur at the aortic area, transmitted to the neck, and a harsh diastolic murmur, transmitted over the entire precordium. No abdominal organs were palpable. There was pitting edema of the feet. Venous pressure was 160 mm. of water.

The urine was normal, the hemoglobin was 10 Gm. per 100 c.c., and the erythrocytes were 3.3 million per c. mm. The blood urea nitrogen was 9.8 mg. per 100 c.c. Three blood Kline tests were negative. The x-ray film revealed marked enlargement of the cardiac shadow with prominence of the hilar and basal lung markings. The electrocardiogram revealed moderate right axis deviation and low T waves.

Therapy included bed rest, low-salt diet, digitalis, morphine and Mercuzanthin. By March 9, 1946, the patient was well compensated and discharged to the outpatient department, which she visited only once shortly after her discharge from the hospital.

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On July 3, 1948, she was readmitted to the hospital. She had been under the care of her family doctor, who had treated her with a maintenance dose of digitalis, Mercuhydrin, and a low-salt diet. The dyspnea, orthopnea, and pedal edema had become progressively worse during the two months prior to the second admission. Pronounced orthopnea was present. The temperature was 98.6° F., the pulse rate was 102, the blood pressure was 150/80, and the respiratory rate was 35. The neck veins were distended. There were crepitant râles at both lung bases. The murmurs previously noted were unchanged. The liver was palpable five fingerbreadths below the costal margin. There was moderate pitting edema of the feet and legs.

The urine contained two plus albumin and occasional granular casts. The blood urea nitrogen was 36.6 mg. per 100 c.c., the creatinine was 1.3 mg. per 100 c.c. An x-ray film showed marked enlargement of the cardiac shadow and prominence of the pulmonary conus; there was evidence of pulmonary congestion and of fluid at both lung bases. The QRS complexes of the electrocardiogram were small, and notched in Lead II. The P-R interval was slightly prolonged and the T waves low to isoelectric.

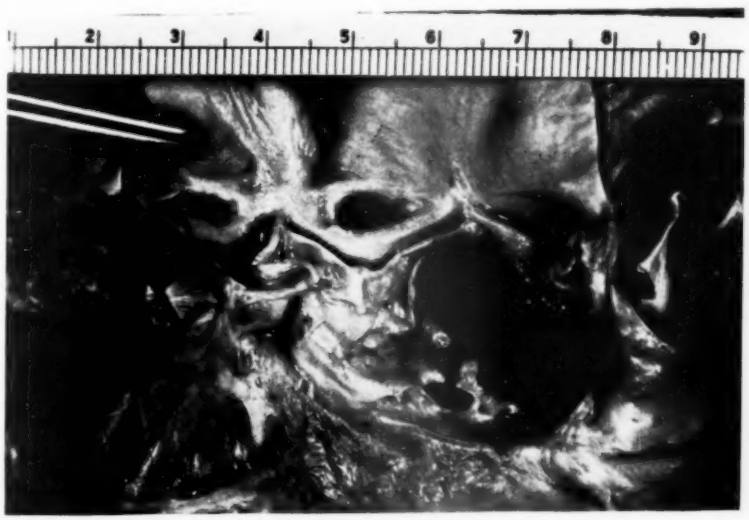

Fig. 1.—A photograph of the aperture of the aneurysm.

The patient received nasal oxygen, a low-salt diet, mercurial diuretics, and digitalis. She did not respond to therapy and died on July 17, 1948.

Post-mortem Findings.—The only lesions of unusual interest were found in the heart and lungs. There were signs of severe passive congestion of the liver, spleen, and kidneys; renal arteriosclerosis of moderate degree; a few small foci of hemorrhage in the adrenal glands. An accessory spleen measuring 2 × 2 × 1.5 cm. was embedded in the perirenal fat about the upper pole of the left kidney.

Heart: The pericardial cavity was obliterated by dense but thin fibrous adhesions. The heart weighed 620 grams; both ventricles were greatly dilated and their walls markedly hypertrophied, the atria were moderately dilated.

Immediately below the base of the aortic valve there was an ovoid aperture in the membranous ventricular septum, measuring 2.5 × 2 cm., in intimate association with the posterior cusps (Fig. 1). These cusps were distorted due to the close proximity of the septal defect, their free edges thickened. In the right cusp there were two fenestrations which looked directly into the septal defect below.

The aperture in the septum led not into the right ventricle, but into a more or less cylindrical sac about 2 cm. in diameter, which extended backward and upward for a distance of 6 cm., lying first behind the ascending aorta, then between the pulmonary artery and left atrium (Fig. 2). The capacity of the sac was 12 cubic centimeters.

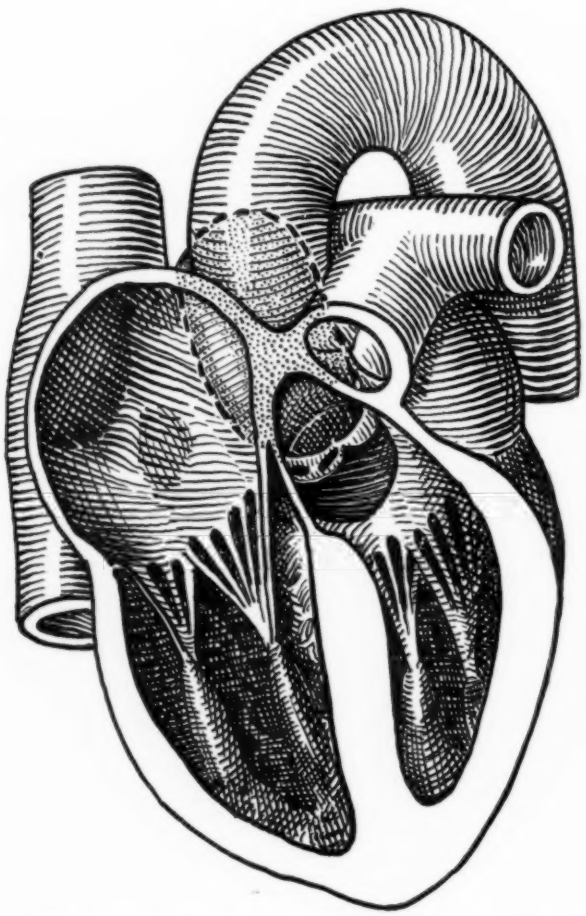

Fig. 2.—A diagrammatic drawing of the heart, great vessels, and exterior of the aneurysm.

The wall of the aneurysm was 2 to 3 mm. thick, and resembled the aorta in gross appearance. The inner surface was grayish-white, glistening and smooth except for occasional small longitudinal wrinkles and a few small plaques resembling those of early atherosclerosis; the outer surface was covered by a thin adventitia-like coat. Microscopic examination showed the wall to consist only of connective tissue: a dense, hyalinized inner layer, a thicker, less compact middle layer in which fibers were arranged in longitudinal strands, and a thin, loose outer layer containing an occasional capillary and sparsely scattered lymphocytes. In several sites small clusters of foam cells, of identical appearance with those observed in atherosclerosis were seen in the inner coat; there were also small scattered foci of calcification.

The tricuspid, mitral, and pulmonary valves were normal. Microscopic examination of the heart muscle revealed hypertrophy, dilated capillaries, and focal hemorrhage. The coronary arteries were patent. The aorta showed only minimal atherosclerotic changes; there was no gross or microscopic evidence of syphilis.

Lungs: The right lung weighed 500 grams, the left, 400 grams. The upper portions of both lungs were of normal appearance and consistency, but the basal portions of the lower lobes were firm and noncrepitant, and on section exuded bloody fluid and revealed alternating areas of hemorrhage and grayish-white consolidation. The trachea and bronchi contained moderate amounts of blood-stained mucoid material.

Microscopic examination revealed marked congestion, and numerous areas of hemorrhage and early infarction. Many alveoli were filled with foam cells and pigment-laden macrophages. In regions of congestion the alveolar septa, thickened by great dilatation of the capillaries, encroached markedly on the air sacs. In many such regions the air sacs and septal borders could not be made out, the lung parenchyma apparently being replaced by masses of capillaries, giving the appearance of numerous hemangiomata. In regions where the capillary masses lay adjacent to branches of the pulmonary artery, invasion of the adventia and occasionally of the media was observed (Fig. 3). In some instances the media appeared to consist only of a ring of small capillaries lying beneath the internal elastic membrane. In other instances small arteries were completely occluded, nests of capillaries replacing the lumina. Similar invasion of the walls of small bronchi was observed, the capillaries extending into but not beyond the musculature.

Many of the small and medium-sized arteries showed marked intimal sclerosis with encroachment upon the lumen, in some instances to the degree of complete occlusion. There were no recent thrombi in the pulmonary arteries. Small spicules of bone were observed in the lung parenchyma in several of the sections, but no cells resembling those of bone marrow were seen.

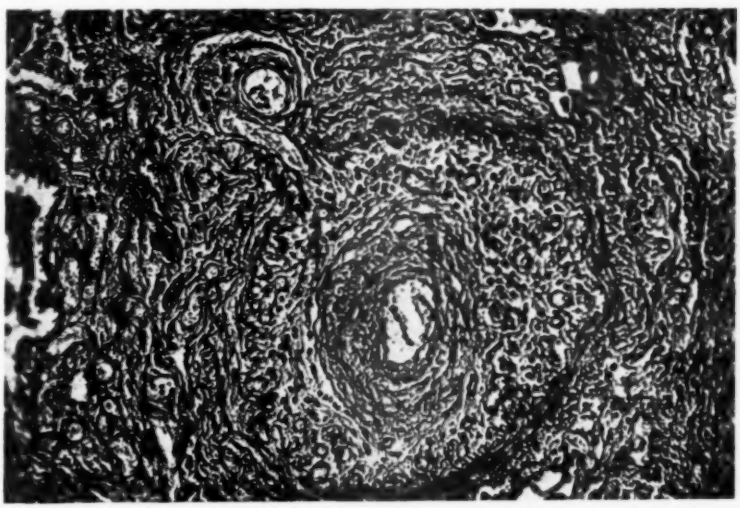

Fig. 3.—Photomicrograph of a section of lung, showing invasion of a branch of the pulmonary artery by the capillary mass.

COMMENT

Aneurysm of the *septum membranaceum* is of little importance—it is rare, and not amenable to clinical recognition. The present case is of interest only because of the unique pulmonary lesions and because of the operation of factors which affected each ventricle separately: aortic insufficiency from distortion and fenestration of the valve; cor pulmonale from obliterative disease of the pulmonary arteries.

Associated anomalies are the rule rather than the exception in cases of congenital aneurysm of the septum. Such anomalies may not be limited to the

heart or vascular system, but may exist in the lungs, biliary tract, and other visceral or somatic structures. Supernumerary spleens were present in the case reported by Cannell,[9] as in ours. However, as far as we can determine, the peculiar vascularization of the walls of branches of the pulmonary arteries and bronchi has not previously been reported. The lesions do not resemble those recently described by Rich[10] in patients with pulmonary stenosis. If the hemangioma-like lesions occurred only in the adventitia of the pulmonary arteries and bronchial walls, they might conceivably represent an attempt at anastomosis between the bronchial and pulmonary systems, secondary to pulmonary arteriosclerosis, although similar anastomoses have not previously been described. However, it appeared that the capillary masses invaded arteries and bronchi only if they chanced to develop in close proximity to them; most of the masses did not seem to be perivascular or peribronchial. It is most likely, therefore, that they are indeed congenital hemangiomata with invasive potentialities.

Obstruction of the pulmonary circulation resulted in part from invasion of arteries by the capillary masses and in part from intimal sclerosis. The pathogenesis of the pulmonary arteriosclerosis is obscure.

SUMMARY

A Negro woman, thirty-nine years of age, presented the clinical picture of congestive heart failure and physical signs of aortic valvular disease. Postmortem examination disclosed a congenital aneurysm of the membranous part of the ventricular septum, associated with fenestrations of the right cusp of the aortic valve and with numerous hemangioma-like lesions of the lungs which invaded the walls of the pulmonary arteries and bronchi.

The authors are greatly indebted to Dr. Edgar Hull for advice and assistance in preparing this article.

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DEFECTIVE INTERAURICULAR CONDUCTION WITH REPORT OF A CASE

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THE diagnosis of interauricular conduction delay rests upon a measured P wave that exceeds 0.12 second in the usual leads. The P wave appears wide, notched, and often tall. Rarely is there a clear separation of the two apical peaks on either side of the notch. When a distinguishable gap intervenes between these auricular waves and when the total duration of the P complex is greater than 0.12 second, it is reasonable to assume that a partial interauricular block exists. Such a clinical example was recently reported by Decherd, Ruskin, and Brindley.[1] Should there be an accompanying block within the auriculoventricular node, the ventricular response would appear late enough to permit unaltered inscriptions of both auricular components. Theoretically, the normal ventricular response to the first auricular excitation wave can obscure or disfigure the registration of the delayed second P component, since Condorelli[2] has cited various separate connections between the sinoauricular and auriculoventricular nodes that by-pass the left auricle. It is felt that such a delayed and unusual activating impulse was operative in producing some of the electrocardiographic features described below.

CASE REPORT

H. N., an adult, white, schoolteacher, 44 years of age, complained of occasional palpitation and aching in the right inframammary region, of three years' duration. As a child, he was afflicted with chicken pox and measles; he never had diphtheria. During his seventh and eighth years he experienced growing pains. Arches were prescribed for the pains in the knees, ankles and feet. Joint-swellings, fevers, chorea, or epistaxis did not appear. Throughout his childhood and adult life he suffered repeated attacks of tonsillitis and sore throats until, at the age of 33, a tonsillectomy was performed. At 7 years he lost a number of teeth accidentally and, for a period of about 30 years, became the subject of severe dental infections and gum suppurations. The sockets of extracted teeth had to be scraped on several occasions. At 21 he had mumps. Five years later he experienced a dull, slow palpitation that occurred irregularly after exertion. In 1941, the Navy rejected him because of the poor dental condition but no mention was made of his cardiac status. In 1942 increasing lassitude appeared. It was then that he learned that his pulse rate was 38. After 1943 recurrent seizures of giddiness became noticeable, particularly after exertion or ingestion of a heavy meal. A peculiar burning sensation in the neck accompanied the attacks of giddiness. Since 1945 he has had dull, non-radiating pain in the right inframammary region after exertion or excessive smoking of cigarettes. Palpitation attended the chest pain and a pulsation, synchronous with the radial pulse, was felt on the right side of the neck. The radial pulse rate varied between 38 and 42 and did not speed up with exer-

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tion. Cough, expectoration, edema, or nocturnal dyspnea were not observed. Reclining on one pillow failed to produce any discomfort, but walking more than one city block at a moderate pace caused dyspnea, palpitation, and chest pain. In 1944 he discontinued smoking cigarettes but continued to take moderate amounts of alcohol at long intervals.

The subject's father died at 63 years of age from hypertension, heart disease, and a cerebral vascular accident. The heart disease was manifested by a slow, uneven beat. A paternal aunt and uncle also succumbed to cerebral vascular disease. The mother is living and well at 72. One brother has been a cardiac patient.

The patient appeared well built and healthy. His weight was 185 pounds; the blood pressure was 148/76. The pulse and ventricular rates were equal at 38 but the rhythm was irregular. The head, neck, lung fields, abdomen, and extremities failed to reveal any abnormalities. The cardiac apical impulse was palpated in the fifth intercostal space beyond the left midclavicular line. The sounds were not altered but a localized, faint, apical, systolic murmur was heard. The second aortic sound seemed louder than the pulmonic. The cervical pulsations were irregular and synchronous with the ventricular beats but venous waves were not visible.

Fluoroscopic examination suggested enlargement of the left ventricle in the posteroanterior and left oblique views. The retrosternal and retrocardiac spaces were not encroached upon by the auricles or the right ventricle. The posteroanterior roentgenogram of the chest indicated moderate enlargement of the left ventricle; the lung fields appeared clear. Visualization of the barium-filled esophagus failed to show any displacement. The Mazzini reaction for syphilis was negative. The sedimentation rate was 12 mm. per hour. Urine analysis revealed the presence of a faint trace of albumin and an occasional finely granulated cast; the specific gravity was 1.019. The hemoglobin was 15.3 Gm.; the red blood count, 4,010,000; the white blood count, 9,800 of which 48 per cent were polymorphonuclears, 46 per cent lymphocytes, 2 per cent monocytes, 3 per cent eosinophiles, and 1 per cent basophiles.

COMMENT

The first electrocardiogram (Fig. 1,*A*) was taken on Oct. 4, 1944. The rhythm was slightly irregular and the rate was 45. In the reproduced tracings, P_1 is flat, P_2 and P_3 are inverted. In CF_1, CF_2, and CF_3 the auricular waves are visibly implanted upon the T waves. The R-P interval measures 0.20 second. The tracing indicates the presence of nodal rhythm complicated by retrograde block.[3] The exact site of nodal automaticity—upper, middle, or lower segment—cannot be established since the location of retarded conductivity cannot be inferred from the tracing. Explaining the irregular rhythm by implicating an augmented vagal tone is quite plausible. Unfortunately, vagal depressants were not employed to test the validity of this statement.

The second electrocardiogram (Fig. 1,*B*) was taken on April 5, 1946. The distribution of the electrical potential prompts serious consideration of the existence of varying but prolonged interauricular and auriculoventricular conduction. The arrhythmia is more marked than in the first instance, and the rate is about 50. In Lead II, the second and third ventricular complexes are preceded by prolonged P waves which begin with positive deflections to be regularly succeeded by negative waves; their amplitude is small. The total duration of the combined polyphasic P elements is 0.28 second. From the end of the auricular wave to the beginning of the ventricular complex 0.20 second elapses. The first ventricular complex of this derivation shows only a preceding elevation of the base line. In Lead III the diphasic P components are seen in all of the beats.

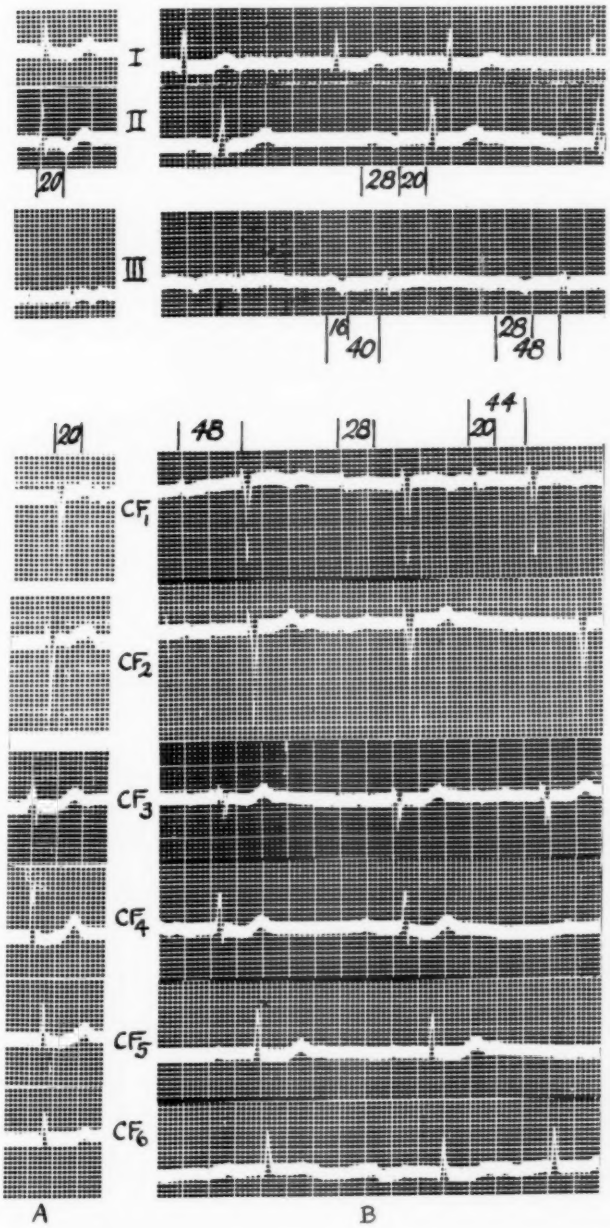

Fig. 1.—*A*, October 4, 1944. The delayed, inverted P waves indicate nodal rhythm complicated by retrograde block. The R-P interval is 0.20 second.

B, April 5, 1946. The auricular complex consists of two separate deflections although the total duration of auricular excitation varies. The P-R intervals fluctuate. (See text.)

(The electrocardiograms shown in Fig. 1, *A* and *B* were obtained through the kindness of Dr. D. T. Bonham, Hempstead, L. I.)

Preceding the second vibratory ventricular complex the P is more prominent in amplitude but abridged (0.16 second). The P-R interval of this cycle is 0.40 second. The remaining diphasic P waves consume 0.28 second and the entire P-R interval measures 0.48 second as in Lead II. In Lead CF_1 the abnormal P waves are clearer and composed of a sharp, upright excursion followed by a slowly rising, upright wave. The first and second auriculoventricular intervals are equal to 0.48 second. The time consumed by these P components is 0.28 second. The third P wave which is superimposed on the U wave is 0.20 second long. Its onset marks a P-R interval of 0.44 second duration. The auricular waves in the remaining leads are of tiny amplitude. The P-P and R-R intervals in the figure vary from beat to beat and do not reveal a reliable common divisor to indicate the presence of sinoauricular block. In Lead CF_2, however, the ventricular complexes are almost evenly spaced.

Although it may be argued that the second part of the auricular deflection represents an auricular T wave, there is much to be said against such an interpretation. As a rule, auricular T waves are ill-defined, of low potential, and rarely so sharply registered. It is unusual to encounter prominent auricular T waves when the P waves are of low or normal amplitude; nor do they vary in duration as do the complexes in Leads III and CF_2, where discernible abbreviations of P are displayed. The total duration of the normal auricular complex from the onset of P to the end of the auricular T wave was found to vary between 0.34 to 0.42 second by Sprague and White.[4] (Other means of recording the auricular potentials of depolarization and repolarization indicate longer $P\text{-}T_a$ intervals.[5,6]) In this tracing the over-all duration measures 0.28 second and less.

It may be suggested that the first wave constituting the P complex represents a sinus nodal excitation wave rather than the action current of the auricular wall. Electrical manifestations of sinus activity, however, are not obtained by any of the standard or precordial derivations, although esophageal and intracavity contacts by carefully applied proximal terminals do present small negative (S) deflections attributable to sinus generation that occur 0.02 second or less before the auricular complex proper.[5,6]

The variations in the width of the P waves indicate that either the delay between the auricles fluctuates, or a different path of conduction is taken by the impulse. The constant pattern of the characters that compose the P wave, however, argues against an alternate route for impulse conduction since, even when there is contraction of the time occupied by the auricular deflections, as in Leads III and CF_1, their form is similar to those that precede or follow. On the other hand, the irregular bradycardia and the varying auriculoventricular intervals lend support to the presence of appreciable but unstable vagal tone. The outstanding feature of this film, nevertheless, is the contrast with the effect of vagal stimulation on the normal auricular muscle. Augmented vagal tone enhances the conductivity and shortens the refractory period of the normal auricles. This improvement in impulse transmission is ordinarily attended by a slower rate of impulse formation in the sinoauricular node and a depressed conduction in the auriculoventricular node. In this electrocardiogram shortening of auricular conduction accompanies contraction of the P-R period—effects that are contrary

to those obtained in normal auricular muscle. Diffuse myocardial disease may be one explanation of these abnormal phenomena if it be accepted that the path of impulse conduction remains stationary.

A clearer insight into the electrical events is found in the electrocardiograms which were taken about two years later (Fig. 2 and Fig. 3). In order to help clarify the electrocardiographic inscriptions, special auricular tracings (Fig. 3)

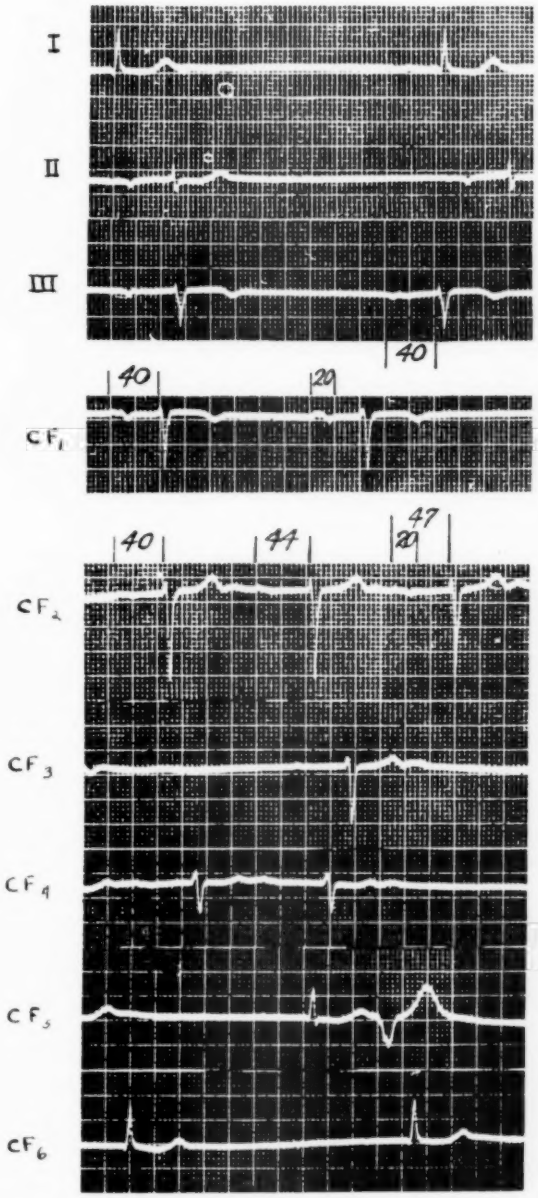

Fig. 2.—February 20, 1948. The auricular complex consists of two dissimilar waves which are again distinctly separated. Auriculoventricular conduction varies.

were taken. The exploring electrode was placed over the third intercostal space to the right of the sternal line and the indifferent terminals were attached to the right upper (CR) and left lower extremities (CF). The tracings are continuous; the cuts were made only to facilitate reproduction. It is regretted that an esophageal lead could not be retained by the patient who expelled it by repeated gagging and vomiting. The auricular complexes in Fig. 2 consume 0.20 second in the standard and precordial derivations. Their form and width are habitually

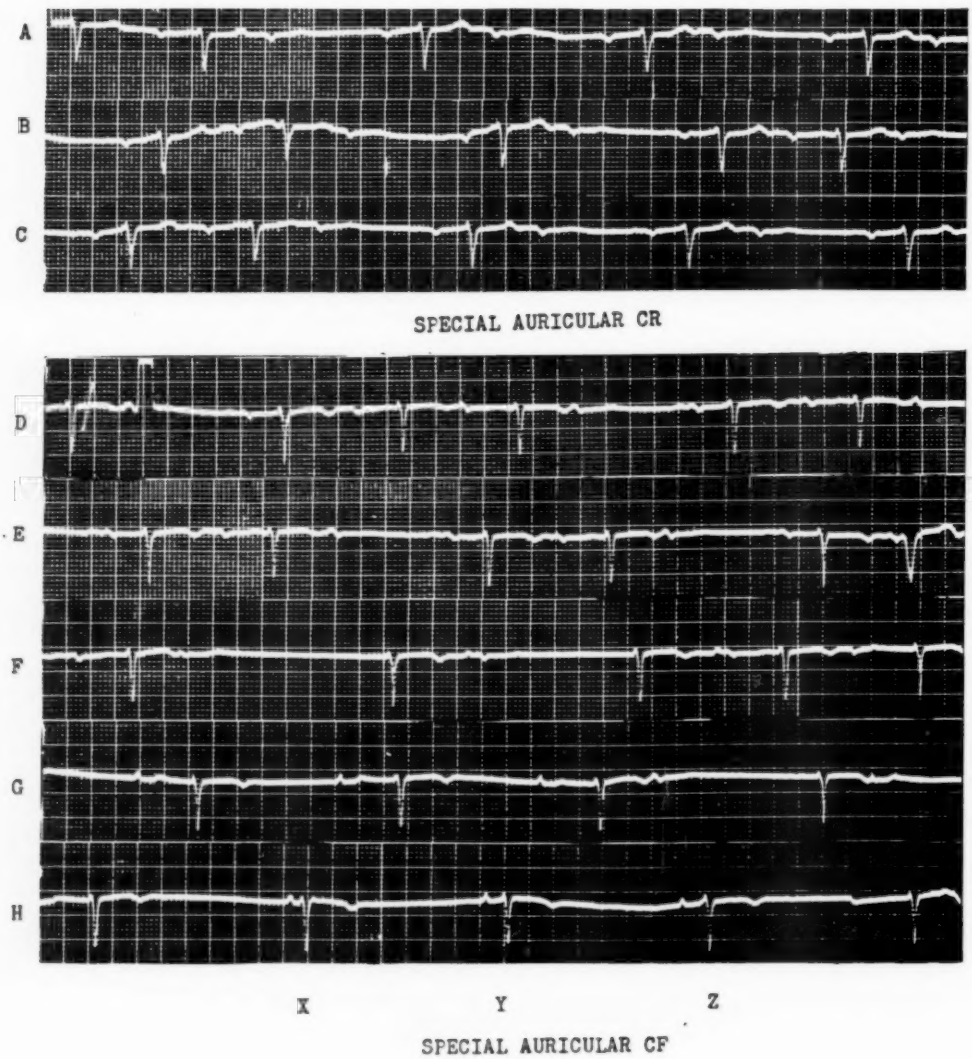

Fig. 3.—February 20, 1948. The form and character of the two P constituents in the special auricular CF derivation changes during this continuous recording. The Wenckebach phenomenon, dropped ventricular beats, and nodal escapes are prominent. *X*, *Y*, and *Z* demonstrate fusion of the ventricular complex and the second auricular component.

retained in all of the respective leads. Though the conductivity through the auriculoventricular node increases from 0.40 to 0.47 second in CF_2, the elapsed time of the P waves remains 0.20 second. Evidently, increments in vagal tone influenced the P-R interval without affecting interauricular conduction. It is proper to indicate, however, that the action current designed P complexes in 1948 that were fundamentally different from those of 1946. It may be inferred, therefore, that a different path of conduction was taken by the impulse as it traversed the auricles to create different P patterns. In that case, the new order of auricular impulse transmission, though defective, might well have proved resistant to the influence of vagal activity.

That a change in vagal tone during the elapsed two years was the cause of the displacement of the earlier impulse pathway is not unlikely. In referring to the development of abnormal P waves during partial heart block, Scherf[7] indicates that altered vagal tone may influence the site of stimulus formation or the course of the stimulus as it engages the auricles.

The first special auricular lead, CR, denotes the presence of 2:1 and 3:2 auriculoventricular block with the dropped ventricular beats ensuing from Wenckebach pauses. The P waves appear inverted, short, uniphasic, and unidirectional. The tracing does not divulge any evidence of delay in the impulse as it pursued its course through the auricles. The proper evaluation of these single, auricular representations is difficult since neutralization and erasure of any positive P components could have been accomplished by the potential of the right upper extremity.

The electrocardiogram obtained from the CF derivation displays the most interesting diversities of auricular conduction. In the first two strips, *D* and *E*, the partial heart block is attended by P waves of a diphasic character lasting 0.12 second. Modification of the P deflections in the strip marked *F* coincides with longer pauses between auricular beats, greater separation of the ventricular pulses, the appearance of nodal contractions, and a higher grade of auriculoventricular block. This set of circumstances fortifies Scherf's contention that increased vagal tone may exercise a profound influence upon the course of the impulse through the auricular walls as well as upon the site of its formation. A slightly more rapid rate of beats occurs in strip *G* where another variant of the form of auricular components makes itself evident. Both are upright though the rapidity of the positive excursion is greater in the first constituent. (There is a striking resemblance of this auricular pattern to that of CF_1, Fig. 1,*B*). The P-R interval remains undisturbed for the first three strokes. From the beginning of the CF tracing to this point the auricular waves not only show a substantial increase in duration (0.12 second, 0.20 second, and 0.24 second) but a decided unlikeness in shape. These continuous alterations of auricular registration afford evidence that various alternate paths of conduction are invaded by the impulse as it traverses the auricles. But, regardless of the course taken by the electrical stimulus, a variable delay in its movement is always to be encountered.

In the last strip of Fig. 3 another revision of auricular behavior appears. The visible P waves consist of single upright excursions that are identical with the initial strokes of the P waves in *G*. Although the conduction between the

auricles and the ventricles is faster than in any one of the previous recordings, it becomes increasingly impeded with every beat (Wenckebach phenomenon). Attention must also be directed to the contrasting forms of the ventricular complexes, *X*, *Y*, and *Z*. Whereas the S wave at *X* ends with a momentary elevation beyond the isoelectric line, the remaining ventricular deflections end abruptly at the base line. At *Z* the R wave, instead of beginning sharply, ascends to its apex by a slowly and gradually developing convexity, an appearance that is identical with the form of the second P constituent in *G*. The gap between the onset of the first and the onset of the second P wave constituent in line *G* measures 0.18 second (interauricular period) and is identical with the distance from the beginning of the auricular deflection to the slight rise succeeding the S wave at *X*. In the next set of complexes that moment (0.18 second) following the P deflection coincides with the inscription of the RS waves. At *Z* the slow emergence of the R wave occurs 0.18 second after the initial P wave; this time precisely marks the end of the interauricular pause referred to in *G*. Hence, in the last line, the second of the auricular components that is so clearly set apart from its preceding fellow in *G*, is rendered almost imperceptible by the earlier delivery of the impulse to the ventricles. If it be assumed that each component of the P expresses the wave of excitation as it passes through the wall of each auricle, the inference to be drawn is that ventricular activation was achieved in a manner unrelated to activation of the second auricle. It appears, then, that interauricular correspondence was firmly maintained after an unalterable delay of 0.18 second, while ventricular activation occurred before, during, and after this period depending upon the degree of defective conduction in the auriculoventricular node. In other words, the action current bifurcated in its course so that one avenue extended to the second auricle and the other avenue, more responsive to vagal stimulation, extended to the ventricles.

The complexes, *X*, *Y*, and *Z* may be considered abnormal insofar as they signify summation or fusion of independent, simultaneous action currents in the ventricles and one auricle. To the list of fusion beats already presented,[8] one may add this rare form created by synchronous stimulation of one auricle and the ventricles. Unlike the common type of fusion beats derived from impulses emanating from two separate foci, these complexes are combination effects of an impulse issued by one center of automaticity that proceeds in two different directions at dissimilar rates of speed.

SUMMARY

A case of defective interauricular conduction attended by auriculoventricular block is presented. Variations in the interauricular and auriculoventricular periods recur irregularly. Displacement of the interauricular pathway coincides with changes in auriculoventricular nodal conduction. The mechanism is postulated whereby the impulse approaches the left auricle and auriculoventricular nodes independently. Fusion beats of the ventricles and one auricle are created by the mechanism described.

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SPONTANEOUS PERFORATION OF AN AORTIC ANEURYSM INTO THE SUPERIOR VENA CAVA WITH SURVIVAL FOR 136 DAYS

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RUPTURE of an aortic aneurysm is a catastrophic event usually resulting in sudden death due to exsanguination or pericardial tamponade. In Boyd's[1] study of 4,000 reported cases the most frequent sites of rupture were the pericardium, left pleural cavity, esophagus, right pleural cavity, and left bronchus. However, when perforation occurs into a great vein or one of the cardiac chambers, death does not ensue immediately, but may be followed by a variable viable period associated with great discomfort, the character and duration of which are dependent upon the nature and exact location of the perforation. With the current remarkable developments in the surgery of the heart and great vessels clinical recognition of the occurrence and localization of such fistulous communications ceases to be of solely academic value. The anatomical or physiological correction of such defects looms in the surgical horizon.

The type of fistulous communication reported occurring most frequently following rupture of an aortic aneurysm is that in which the superior vena cava participates. Less common sites of fistula formation are the pulmonary artery, the right auricle, and the right ventricle. All produce characteristic signs and symptoms and all are diagnosable during life.

The first reported case of perforation of an aortic aneurysm into the superior vena cava was that of Beevor[2] in 1832. In 1882, Damaschino and Lavin[3] reported the case of a 50-year-old man in whom all the accepted criteria for the diagnosis of an arteriovenous communication between the aorta and superior vena cava were present with recovery, apparently due to spontaneous closure of the fistula. Pepper and Griffith[4] (1890) presented twenty-eight cases collected from the literature and reported on one of their own. Little has since been added to their lucid description of the clinical manifestations of this syndrome. In 1939, Armstrong, Coggin, and Hendrickson[5] in a review article reported on ninety-eight cases collected from the literature and added two of their own. Since then an additional ten cases of spontaneous arteriovenous aneurysm, involving the aorta and superior vena cava, have been reported[6-15] making a total of 110. Survival for more than four months, with close clinical documentation throughout, and the direct observation of the lesion during exploratory thoracotomy lends justification for the reporting of this additional case.

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CASE REPORT

The patient was a 41-year-old, white, male truck driver who was admitted to Mt. Sinai Hospital complaining of progressive swelling of the upper half of his body of three weeks' duration. At the age of 20 he had contracted syphilis which was treated for a period of nine months by means of "arm and hip" injections. Other than this, his past medical history was noncontributory. He was completely asymptomatic up to three weeks before admission, when, upon arising from an afternoon nap, cyanotic swelling of his neck, face, and hands was noted. During the ensuing three weeks the edema gradually increased to involve his thorax and upper abdomen. This was associated with the onset of progressive exertional dyspnea and orthopnea. One week before admission ankle edema became manifest. In contrast to that present in the upper half of the trunk, the ankle edema disappeared with bed rest. Except for mild frontal headaches pain was not experienced.

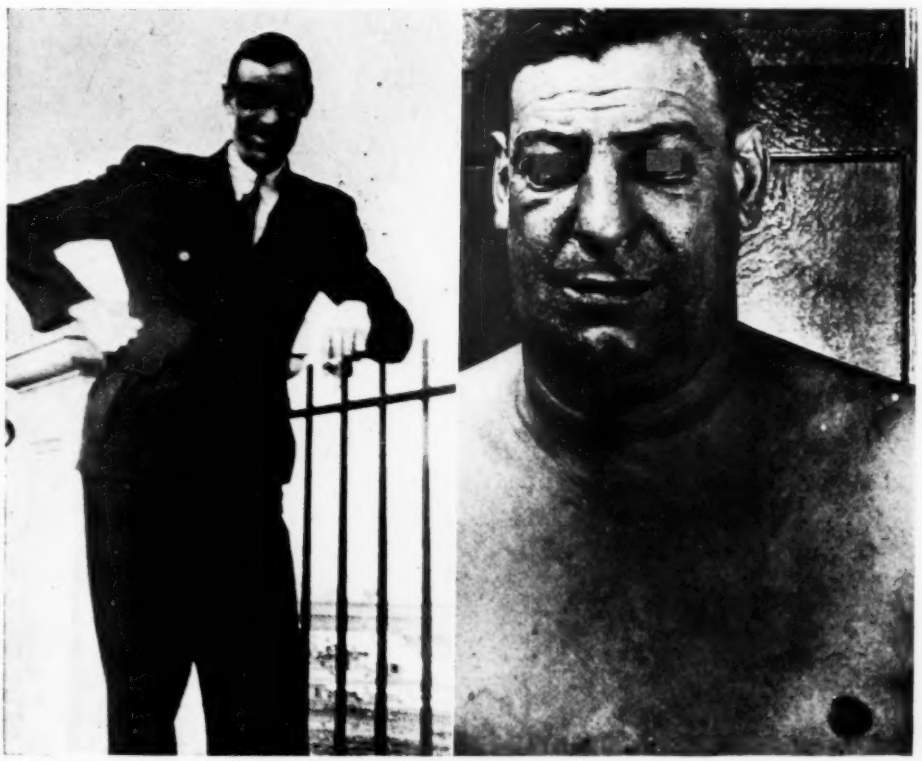

Fig. 1.—The picture on the left was a casual photograph taken of the patient approximately one year before onset of the present illness. The photograph on the right was taken about three weeks after his admission to the hospital.

Physical examination on admission revealed a drowsy, moderately uncomfortable man with profuse diaphoresis and a diffuse brawny edema of the entire upper half of the body associated with many dilated veins and venules over the thorax. The skin over the edematous area had a dusky, cyanotic hue. A sharp line of demarcation was present just above the level of the umbilicus, making the lower half of the trunk appear ludicrously thin by contrast (Figs. 1, 2, and 3). Moderate dyspnea and marked orthopnea were present. The conjunctivae were chemotic. Firm, nontender, discretely enlarged lymph nodes were present in both axillae. Coarse, sonorous,

expiratory râles were heard throughout both lung fields. There was some dullness and decreased transmission of fremitus and breath sounds at both lung bases posteriorly. Examination of the heart revealed the point of maximum impulse to be in the fifth intercostal space, 4 cm. medial to the anterior axillary line. Cardiac percussion dullness was moderately increased both to the right and the left. The heart sounds were distant. The aortic second sound was greater than the pulmonic second sound. Regular sinus rhythm was present with numerous extrasystoles. At the third right intercostal space, just lateral to the right parasternal line a loud continuous murmur and thrill with systolic accentuation were present with maximum transmission to the right infraclavicular region and axilla. Blood pressure readings were equal in both upper extremities and averaged 120/58 mm. Hg. The liver edge was palpable three fingerbreadths below the right costal margin. An old, healed scar was present on the glans penis.

Serological studies revealed a 2+ blood Wassermann and a 3+ Kahn. On lumbar spinal puncture, pressure was 540 mm. with pulsations of 6 to 8 mm. of spinal fluid. There were 27

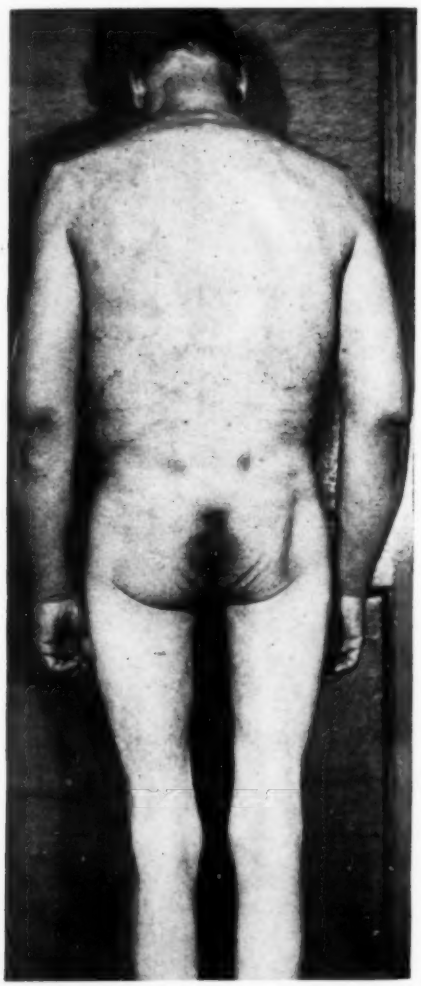

Fig. 2.—A full-length photograph of the patient three weeks after admission to the hospital showing the marked edema of the upper half of his body with a sharp line of demarcation just below the waist line. Note the wasting of the gluteal region and the thin legs when contrasted to the arms and chest.

lymphocytes per mm. of spinal fluid, a 1+ Pandy test, a total protein of 13 mg. per 100 c.c., a 4+ Wassermann, a ±globulin test and a colloidal gold curve of 33321100000.

A saccharin circulation time determined from a vein on the back at the level of the sixth thoracic vertebra was 15 seconds. An ether circulation time from the same site was 7.5 seconds. The venous pressure was 30 cm. of blood, with a rise to 42 cm. upon straining. Venous pressures and circulation times were compared in the upper and lower extremities, with and without the application of an abdominal tourniquet, and are presented in Table I. These results indicate increased venous pressure and obstruction to flow in the superior, but not in the inferior, vena caval systems.

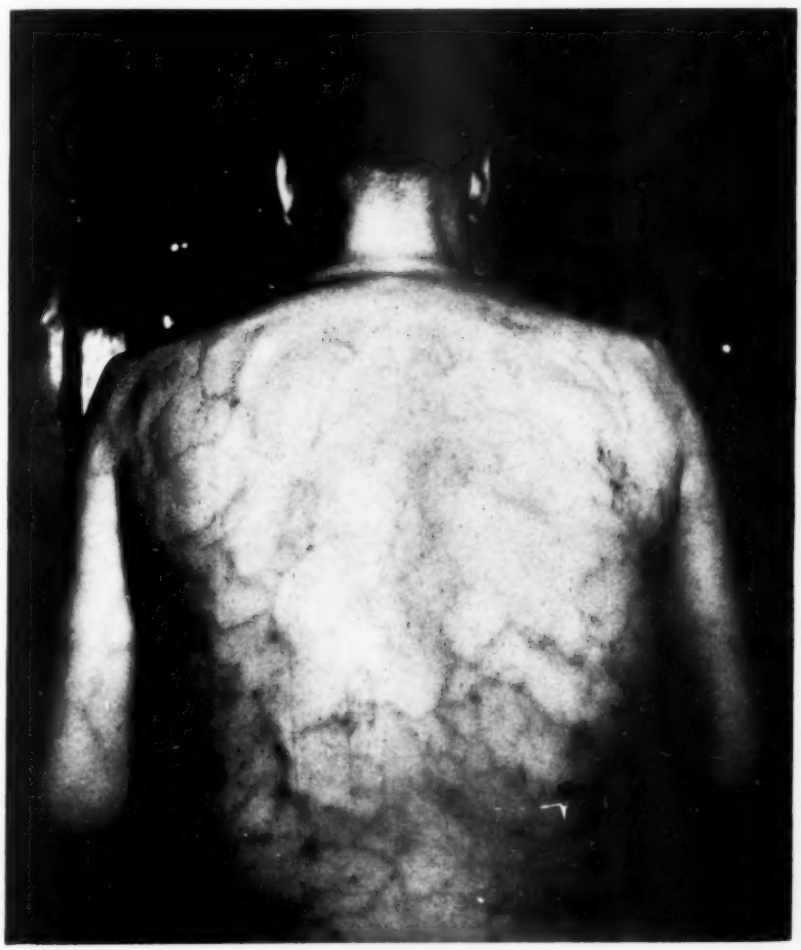

Fig. 3.—An infrared photograph of the patient's back revealing the marked collateral venous circulation.

A roentgenogram of the chest (Fig. 4) revealed a fairly well-circumscribed mass in the anterior-superior mediastinum extending to the right. On fluoroscopy the mass was seen to pulsate. Roentgenkymography revealed the mediastinal mass as a pulsatile one. A marked ventricular systolic thrust was present.

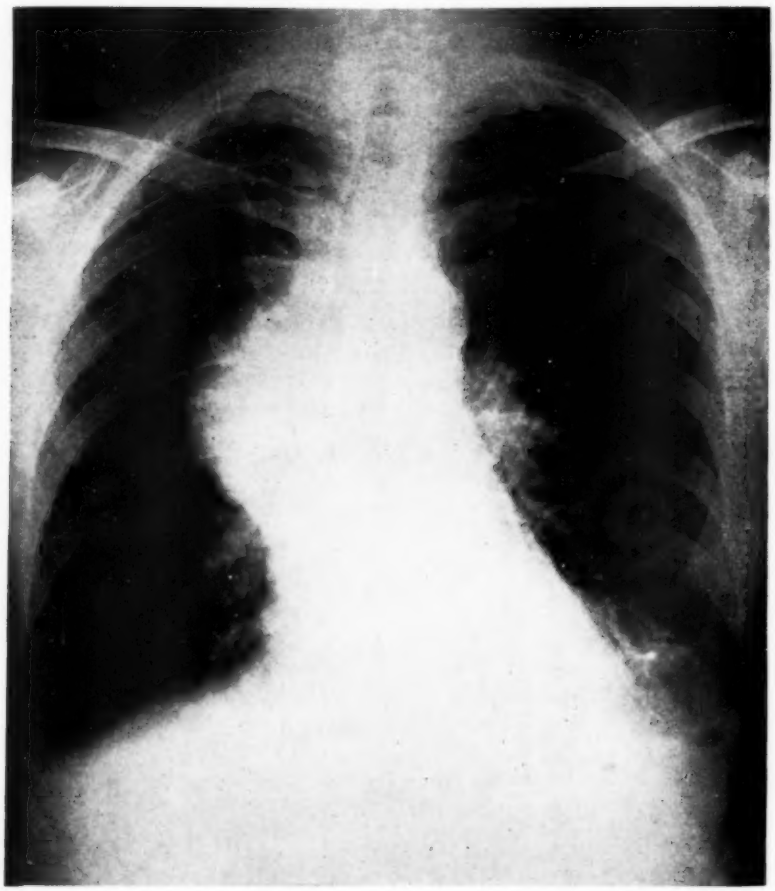

Fig. 4.—X-ray film of chest. The mass in the region of the ascending aorta was seen to pulsate on fluoroscopy. Note the small collection of fluid at both lung bases.

TABLE I. VENOUS PRESSURES AND CIRCULATION TIMES

LIMB	VENOUS PRESSURES		CIRCULATION TIMES	
	WITHOUT ABDOMINAL TOURNIQUET (CM. OF BLOOD)	WITH ABDOMINAL TOURNIQUET (CM. OF BLOOD)	ETHER (SECONDS)	SACCHARIN (SECONDS)
Left Arm	34.6	48.8	23	No end point
Right Leg	6.0	6.0	15	18

Angiocardiography was attempted by the injection of Diodrast into the right antecubital vein. The injection mass was abruptly halted just distal to the region of junction of the innominate veins. This obstruction appeared to be located at the upper border of the mass of the mediastinum. Numerous collateral veins were visualized, but the Diodrast did not enter the heart.

A phonocardiogram revealed systolic and diastolic murmurs of moderately high frequency occupying the entire cardiac cycle and best heard over the aortic area.

Course.—At the time of admission the patient appeared preterminal. For several days, in spite of digitalis therapy, oxygen administration by a Boothby, Lovelace, Bulbullian mask, and mercurial diuresis, his orthopnea, cyanosis, and drowsiness became more severe. However, after about one week he started to manifest gradual improvement. The palpable liver edge receded, and the superficial epigastric veins became more prominent. Apparently adequate collateral circulation was being established. Improvement was so conspicuous that the patient was allowed out of bed by the twenty-first hospital day. This improvement was short-lived, however, as during the fifth hospital week he again developed signs of congestive heart failure with increasing dyspnea, orthopnea, weight gain, ankle edema, and pulmonary congestion. During the eighth hospital week the right superficial epigastric vein was seen to pulsate for the first time. All the diagnostic criteria for the diagnosis of an arteriovenous aneurysm between the aorta and superior vena cava had thus been established.

Because of progressive heart failure and the otherwise hopeless prognosis an exploratory thoracotomy was performed on the seventy-fifth hospital day by Dr. Arthur S. W. Touroff with the hope of being able to correct some of the hemodynamic abnormalities.

A right-sided transpleural approach was used. As the structures of the chest wall were divided profuse bleeding was encountered from innumerable dilated vascular channels. When the lung was permitted to collapse a globular fusiform dilatation of the first portion of the aorta was seen. It measured four inches in diameter. The expansion was partly intrapericardial and partially suprapericardial, gradually tapering off into the first portion of the aortic arch. The superior vena cava was only moderately dilated. A coarse thrill was palpable in the vena cava, which was transmitted both up toward the neck and downward to the base of the heart. The azygos vein was markedly dilated. As pressure was applied to the vena cava about three-fourths of an inch above the entrance of the azygos vein the thrill disappeared abruptly and the cardiac rate slowed appreciably. It was apparent that the arteriovenous communication was present at this point and was of small enough caliber to be temporarily occluded by fingertip pressure. On the basis of the anatomical findings operative intervention appeared unwarranted. The thorax was therefore closed.

The postoperative course was a stormy one. Because of the numerous vascular channels which were divided recurrent right hemothorax ensued, requiring frequent chest aspirations. In spite of prophylactic penicillin administration empyema developed. *Escherichia coli* and *Streptococcus faecalis* were both cultured from the empyema contents. Thoracotomy was performed on two separate occasions to provide adequate drainage. In spite of blood transfusions and other supportive measures the patient's condition steadily deteriorated. The patient died on the forty-first postoperative day, 136 days after the acute perforation of an aortic aneurysm into the superior vena cava.

Post-Mortem Examination.—Examination of the heart revealed moderate dilatation and hypertrophy of all chambers of the heart, especially of the right auricle. About 4.5 cm. above the aortic ring there was an aneurysmal sac of the aorta, measuring 6 cm. in its longitudinal diameter and 8 cm. in its transversal diameter. It extended to just beyond the origin of the left subclavian artery and was filled with freshly clotted blood (Fig. 5). The sac bulged to the right, extending anteriorly and posteriorly, stretching the superior vena cava and mediastinal tissues over its surface. At the summit of the sac, to the right and anteriorly there was a circular perforation, 8 mm. in diameter, through which the aneurysm communicated with the superior vena cava (Fig. 6). The wall of the aorta was considerably thinned in this area. An oval area of lamellated sclerosis, 9 mm. in diameter was present on the intima of the superior vena cava opposite the arteriovenous communication, which was about 1.2 cm. above the entrance of the azygos vein

into the cava (Fig. 7). There was no evidence of thrombosis in either vein. The vena cava appeared moderately dilated and thickened, measuring 5 cm. in diameter, both above and below the site of perforation. The intima of the aorta presented the characteristic wrinkling of syphilitic aortitis (tree-bark appearance).

Except for numerous dilated venous tributaries of the azygos vein, empyema of the left pleural cavity, central liver congestion, and a prepyloric gastric ulcer, the remainder of the findings were not remarkable.

Fig. 5.—Photograph showing the aneurysmal sac filled with freshly clotted blood. Below the aneurysm the wrinkled (tree-bark) appearance of the aortic root is evident.

Microscopic examination revealed perivascular interstitial fibrosis of the myocardium and varying degrees of medial destruction of the wall of the aorta. The wall of the aneurysm contained no media. The adventitia contained numerous small vessels with thickened intima and perivascular lymphocytic infiltrations. The superior vena cava adjacent to the aneurysm revealed complete replacement of its usual structure by a looser fibrous connective tissue. The target area of the superior vena cava was seen as an elevated patch of intima with hyaline change and underlying fibroblastic proliferation.

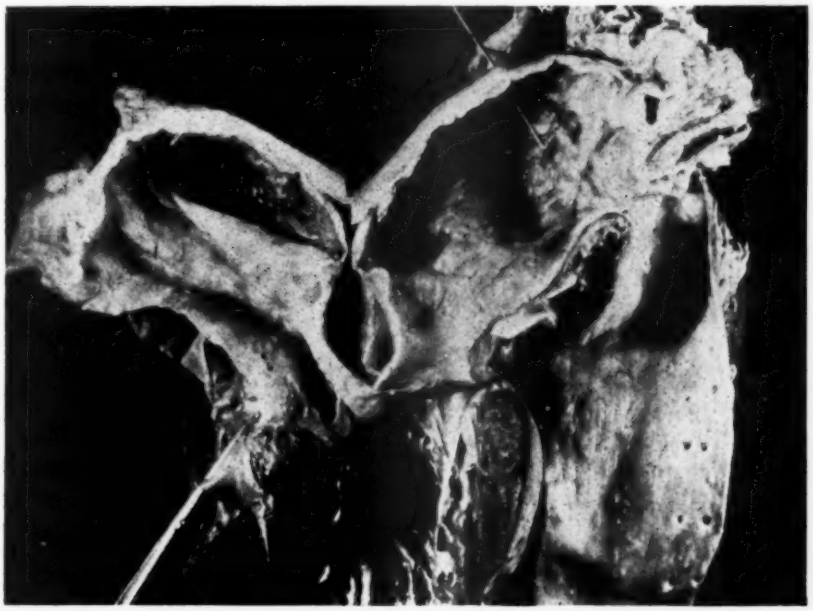

Fig. 6.—The probe is seen passing through the arteriovenous communication near the summit of the aneurysm. The wall at this point represents the combined thickness of the aorta and superior vena cava.

Fig. 7.—Photograph of the superior vena cava opened on its course to the right auricle (on the left). The probe is presenting through the mouth of the azygos vein. The fistula is seen 1.2 cm. cephalad opposite which is the target area (white arrow).

DISCUSSION

All the criteria for the diagnosis of a fistulous communication between the aorta and superior vena cava were fulfilled in this case. These are:

1. Sudden onset of a severe superior vena caval syndrome with edema, cyanosis, and increased venous pressure limited to the upper half of the body.
2. Positive blood serology.
3. A loud continuous murmur and thrill with systolic accentuation exhibited with greatest intensity over the region of the ascending aorta.
4. The presence of a pulsating mediastinal mass in the region of the ascending aorta.
5. Cardiovascular dynamics of an arteriovenous aneurysm with an elevated pulse pressure.
6. Pulsating veins and spinal fluid.

Armstrong, Coggin, and Hendrickson[5] correlated the site of perforation into the superior vena cava with the distribution of the edema. They found that when perforation occurs above the entrance of the azygos vein, swelling and cyanosis were limited to the head, neck, and upper extremities; when below the azygos vein there was extension of the edema to the thoracic wall and usually hydrothorax. Since the subject of this report exhibited edema down to the waist and pleural effusions soon after the onset of the accident, it was our clinical impression that the fistulous communication occurred below the mouth of the azygos vein within the pericardial reflection. The operative and post-mortem findings proved this to be wrong. The fistula was about 1.2 cm. above the entrance of the azygos vein, although still within the pericardial reflection. The reason for involvement of the thorax with edema and cyanosis, as well as the head, neck, and arms, was apparent, however. The position of the aortic aneurysm was such as to produce obstruction of flow in the superior vena cava below the azygos vein ostium, which, while causing extension of the edema and cyanosis, delayed for some time the onset of severe right-sided heart failure and explains the relatively normal venous pressures in the inferior vena caval system late in the course of the disease. The azygos vein apparently bore the brunt of the fistulous blood flow. This accounts for the pulsating spinal fluid and the pulsating right superficial epigastric vein. The azygos vein communicates directly with the latter through the right intercostal veins and with the spinal canal through the vertebral veins. It is of interest that in only 12 per cent of the reported cases of this syndrome were pulsating veins seen.

When perforation of the aortic root occurs into the right auricle the clinical picture is quite different.[16] There is a sudden onset of a sense of smothering and fullness in the chest and upper abdomen, but cyanosis and swelling of the face does not occur. The liver enlarges rapidly, becomes painful, and pulsates. The continuous murmur with systolic accentuation is best heard in the midsternal region and the diastolic component is transmitted along the right sternal border and downward toward the liver. The electrocardiogram will reveal evidence of right axis deviation and paroxysms of atrial arrhythmias.

When perforation occurs into the right ventricle survival is usually of brief duration.[17] The onset is sudden and distress is severe with the rapid develop-

ment of severe congestive heart failure. The continuous murmur is heard with maximum intensity just to the left of the sternum in the third intercostal space. Severe angina, due to coronary artery compression and left bundle branch, or intraventricular, conduction defects may be present.

The distinctive features of perforation into the pulmonary artery are the sudden onset of continuous and severe breathlessness out of all proportion to the physical findings of pulmonary congestion, the preponderance of right-sided heart failure, and the presence of a loud continuous murmur and thrill with maximum intensity 1 to 3 cm. to the left of the sternum in the third intercostal space. Roentgenograms will reveal evidence of an aneurysm of the ascending aorta and cardiac enlargement of the mitral type rather than the aortic. The hemodynamics of aortic insufficiency are present without an Austin Flint murmur. Cyanosis occurs but is not as severe as that encountered with perforation into the superior vena cava.

SUMMARY AND CONCLUSIONS

1. A case of spontaneous rupture of an aortic aneurysm into the superior vena cava with survival for four months is described.

2. When an aortic aneurysm perforates into the heart or any of the adjacent great vessels the localization of the resulting fistula is possible on the basis of clinical and laboratory findings and may be of some practical value since surgical amelioration is now a possibility.

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SITUS INVERSUS WITH LEVOCARDIA

A Case Report

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SITUS inversus with levocardia is usually associated with bizarre cardiac anomalies. Although the heart is apparently normal in its location within the thorax, it is analogous to a dextrocardia associated with a normal position of the abdominal organs.

This case is reported because it is a rare condition which must be considered in the differential diagnosis of congenital cardiac anomalies which are amenable to surgical improvement or correction. A newborn infant was undergoing studies to determine the cause of persistent vomiting. The cause proved to be a duodenal atresia which was subsequently corrected by surgical intervention. The x-ray showed the heart to be apparently in its usual location in the left hemothorax but the abdominal viscera were transposed. Below is a description of the clinical course, surgical, and autopsy findings.

CASE REPORT

A. S. was a boy of Japanese parentage born at term by normal delivery on Dec. 12, 1947. The birth weight was 7 pounds, 14 ounces. Physical examination immediately after birth revealed no abnormalities other than a loud systolic murmur heard over the entire precordium. The infant vomited all feedings and the vomitus was green. He was given daily hypodermoclyses of normal saline. Roentgenograms on the sixth day of life revealed the stomach to be in the right side and markedly dilated with gas. There was no gas in the small bowel. The heart was on the left side of the thorax and was normal in size. A diagnosis of duodenal atresia was made and the infant was operated upon under intratracheal anesthesia by Dr. Franklin I. Harris.

Upon opening the abdomen, the liver and gall bladder were found in the left upper quadrant. The spleen was in the right upper quadrant. The stomach and the first part of the duodenum were dilated. The duodenum was intra-abdominal and supported by a mesentery. The third portion of the duodenum ran from left to right, and was posterior to a mesocolon which supported the entire colon; the cecum and appendix were in the left lower quadrant. There were multiple peritoneal bands passing from the lateral abdominal walls to loops of bowel and also between loops of intestine.

The third part of the duodenum was anastomosed to the first portion of the duodenum and the pyloric portion of the stomach. The infant withstood the operation very well. He received penicillin, a transfusion of whole blood, and parenteral fluids postoperatively. On the first postoperative day a generalized edema developed associated with fine râles in the lungs due to pulmonary edema. The infant expired forty-eight hours after the anastomosis was performed.

Autopsy Findings.—Autopsy was performed two hours after death.

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Macroscopic Description: Only findings related to the congenital defects will be described. The abdominal viscera were oriented as described previously. The thoracic organs were apparently normally placed, with the heart lying on the left side, the three-lobed lung on the right, and the two-lobed lung on the left. The heart was globular in shape and moderately enlarged. It weighed 21 grams. The heart had four chambers consisting of right- and left-sided auricles and right- and left-sided ventricles. The superior and inferior venae cavae entered the right-sided auricle. This auricle communicated with the left-sided auricle through a partially patent foramen ovale which was covered in part by a membrane. The auricles were of normal size. The right-

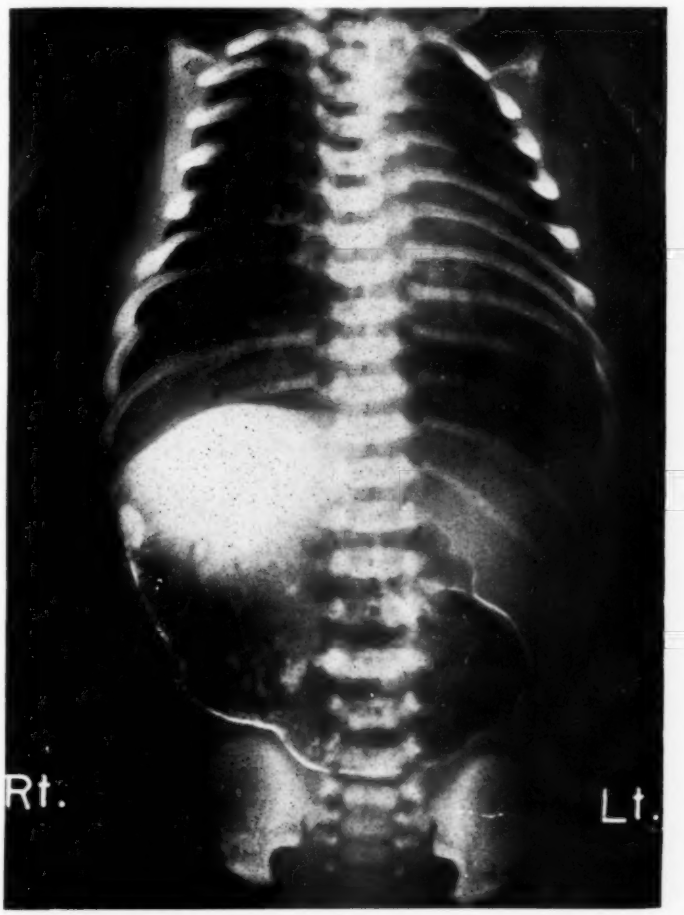

Fig. 1.—Posteroanterior roentgenogram of the chest and abdomen. Heart is enlarged with apex toward the left. The stomach is markedly dilated with no gas or barium entering the duodenum.

sided auricle connected with the right-sided ventricle through a valve possessing two leaflets; the aperture of this valve was of normal size. The right-sided ventricle had a myocardium measuring 0.4 cm. in thickness. The aorta arose from this ventricle. The aortic valve was of normal diameter and had three semilunar cusps, one lying anteriorly and two lying posteriorly. The coronary arteries arose behind the two posterior cusps. The three main branches of the aortic arch arose normally. The ductus arteriorus was freely patent, communicating between the aorta and the pulmonary artery.

There were three pulmonary veins which entered the left-sided auricle. This auricle communicated with the left-sided ventricle through a bicuspid valve of normal diameter. It also communicated with the right auricle through the partially patent foramen ovale, as previously described. The left-sided ventricle was markedly dilated; its myocardium was 0.3 cm. in thickness. From this ventricle arose the pulmonary artery, which was moderately dilated, as was also the three-cuspid pulmonary valve orifice. The two ventricles communicated by a defect in the antero-superior portion of the ventricular septum. The defect was 0.5 cm. in diameter.

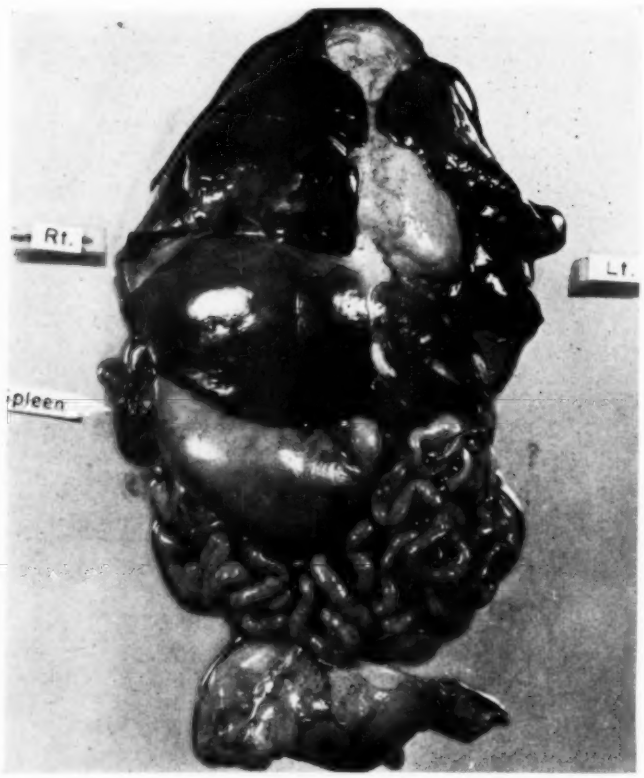

Fig. 2.—Photograph of the thoracic and abdominal viscera showing the lungs and heart to be in normal position with the stomach and spleen on the right. Note that the three-lobed lung is on the right side of the chest.

The gastro-duodenostomy was intact and possessed an adequate stoma. In the second portion of the duodenum, the lumen was occluded by a membrane 1.0 mm. in thickness. The duodenum at this point was slightly constricted. The gastrointestinal tract contained no other intrinsic abnormalities.

Microscopic Description: Normal tissues will not be described. The membrane in the duodenum was covered on each side by duodenal mucosa with a middle layer of smooth muscle. The central hepatic sinusoids were congested and the peripheral liver cells contained large fat globules. The distal convoluted tubules of the kidneys contained numerous deposits of material which stained selectively as calcium.

Course of the Blood: The blood entered the right-sided auricle through the venae cavae. From there it went into the right-sided ventricle by means of a bicuspid orifice. From the right-sided

ventricle it went through a normal aortic valve into the aorta where it was distributed normally, returning by way of the venae cavae to the right-sided auricle.

The blood from the lungs entered the left-sided auricle by the three pulmonary veins from where it went through a bicuspid orifice into the left-sided ventricle. From here it passed through the pulmonary orifice into the pulmonary artery to the lungs from where it returned to the left-sided auricle by means of the pulmonary veins.

These two independent circulations were incompatible with life unless accompanied by some means of transmission of blood from one circuit to another. This was accomplished by three means: (1) a partially patent foramen ovale, (2) an interventricular septal defect, and (3) a patent ductus arteriosus. Bing[4] has shown that in a septal defect there is a flow of blood in both directions, although the main flow may be in one direction.

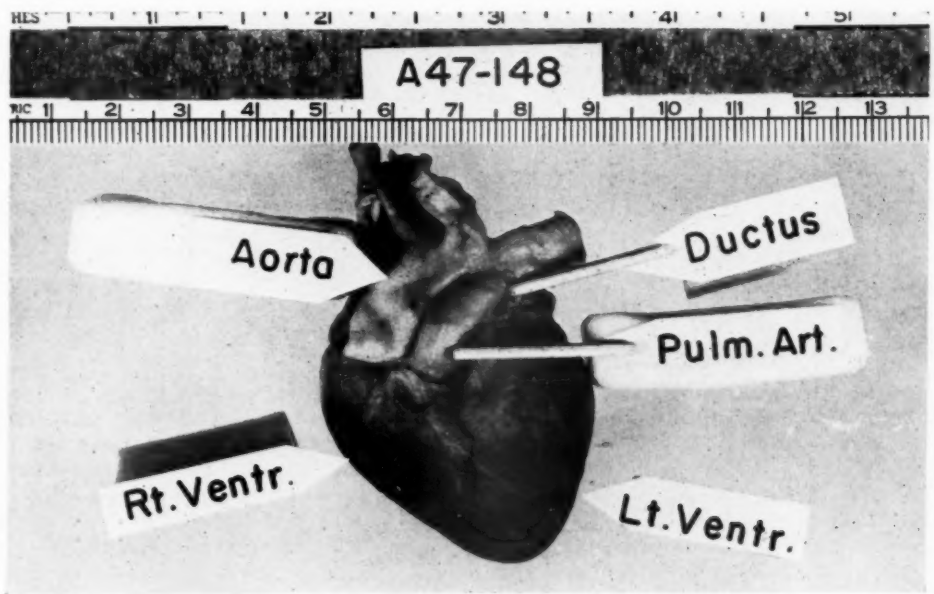

Fig. 3.—Photograph of the heart as it appeared in situ. It shows the aorta leaving the right ventricle and the pulmonary artery leaving the left-sided ventricle. The patent ductus connects the two vessels.

DISCUSSION

This case is of interest because the heart, although in its usual position in the body radiologically, is abnormally placed in relation to the abdominal viscera. One of us, S.J.R., has seen a similar case also associated with similar anomalies of the heart. Taussig[2] has described three such cases and points out that a situs inversus of the abdominal viscera with a heart which occupies an apparently normal position usually means a complete reversal of all organs and that the heart has been rotated back to the left.

Fourteen other cases of situs inversus with levocardia have been described up to 1947. It is of interest in that eight of these were associated with a transposition of the atria as well as the great vessels, in other words, a corrected transposition. The oldest patient with such a defect lived to the age of seventeen

years; another lived to five years and died after attempted surgery to the heart. Most, however, have expired in the first few days of life.

SUMMARY

1. A case of situs inversus with levocardia associated with duodenal atresia is presented.

2. A review of the literature indicates that seventeen similar cases have been reported.

3. All such cases have had bizarre anomalies of the heart and great vessels, usually either a transposition of the great vessels or a corrected transposition with reversal of the atria.

The authors wish to thank Dr. W. P. Lucas and George Sherman for allowing them to report this case.

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Notice

It has been recently announced that the papers presented at the First International Cardiovascular Congress, which is being held in Paris from September 3 to 9, 1950, will be published in the *Archives des maladies du coeur*.

Information has also been received that The International Society for Internal Medicine will hold its first formal meeting in Paris immediately following that of the Congress. The program of the Society is being prepared under the direction of Professor A. Gigon, 1, Hebelstrasse, Basle, Switzerland, and Professor Svartz, Karolinski Sjukhuset, Stockholm 60, Sweden.

Book Reviews

DISEASES OF THE HEART. By Charles K. Friedberg, M.D., Associate Physician, Mount Sinai Hospital, New York; Lecturer in Medicine, Columbia University. Philadelphia and London, 1949, W. B. Saunders Company, 1,081 pages and 79 figures. Price $11.50.

During the past century, there have been written, with increased frequency, books dealing with diseases of the heart or with the wider field of circulation in general. The texts of most of these have been influenced by some particular advance in our knowledge, whether physical signs, pathological anatomy, polygraphic tracings and their interpretation, electrocardiography, and, more recently, physiology and physiological pathology. Some authors have approached the subject from the particular to the general, while others have, more rarely, followed the reverse plan of dealing first with the general and then with the particular.

The present author has, to a large extent, followed the latter plan. He has begun with circulatory failure in general. He has introduced the subject with a concise account of certain important physiological considerations, and the cardiac and circulatory compensations that are brought to bear in the early stages of these disturbances. This same method of exposition is continued, and the influence of circulatory failure on the circulation in general and of disturbances in the peripheral circulation upon the functional capacity of the heart itself is shown. In this manner, he has built up a logical and open-minded review of the many factors which have been considered to enter into the complicated series of vicious circles which seem to govern the initiation and perpetuation of congestive heart failure.

In a clear and logical manner, he then deals with the treatment of congestive heart failure. This is a well-balanced discourse. He is not dogmatic but rather he weighs the different therapeutic measures to attain a particular objective. These therapeutic measures are integrated one with the other as specific indications may warrant.

The author brings out clearly the difference between congestive heart failure and acute circulatory failure. He devotes a brief section to this important but frequently confused circulatory accident. The purist might hold that peripheral circulatory failure has no place in the consideration of cardiac disease. On the other hand, the more congestive heart failure is studied in relation to peripheral imbalance, the more does it become obvious that congestive cardiac failure cannot be considered as a local disease of the heart itself.

Part II deals with cardiac arrhythmias. This subject is taken up after the classical fashion and there is nothing unusual or original in its presentation.

Part III deals with coronary circulation and disturbances in the cardiac blood supply. This is well constructed and well documented and covers the subject quite adequately in so far as our present knowledge is concerned. One would have hoped that greater consideration would have been given to the pain which plays such an important role in the diagnosis of coronary disease. It would have been particularly helpful if the pathways of pain associated with those conditions which are to be differentiated from angina pectoris were dealt with in detail. In fact, it is noted that pain, as such, does not appear in the index.

Part IV is devoted to structural abnormalities of the heart and deals chiefly with pericarditis, myocarditis, valvular disease, and anatomical lesions. With few exceptions, this leads to a fair amount of repetition as, except for pericarditis and acute endocarditis, they are chiefly considered from the point of view of their etiology, their recognition, and the manner in which they may contribute to congestive heart failure. There is no doubt that this aspect of heart disease should be included in the text, but it still remains a matter of opinion as to whether it would not have been better to relate them more closely with Part I, or congestive heart failure.

Heart disease from the etiological point of view is considered in Part V. This includes principally congenital abnormalities, rheumatic fever, bacterial endocarditis, syphilis of the heart and aorta, and the heart in infections and in hypertension. Acute and chronic cor pulmonale are also considered in some detail as are the heart and circulation in diseases of the ductless glands, anemia, and metabolic and nutritional disturbances. Short sections are given over to traumatic heart disease, cardiac tumors, and functional manifestations, while in Part VI, heart disease in pregnancy, surgical procedures, insurance and medico-legal problems are dealt with concisely.

Except for electrocardiograms and a few roentgenograms, the text is conspicuously devoid of illustrations. The bibliography is extremely well covered and the index is good.

The author is to be congratulated on the accomplishment of a difficult task, and the publishers commended for affording the reader a good format, paper, and printing.

J. C. M.

ELECTROCARDIOGRAPHY, FUNDAMENTALS AND CLINICAL APPLICATION. By Louis Wolff, M.D., Visiting Physician, Consultant in Cardiology and Chief of the Electrocardiographic Laboratory, Beth Israel Hospital; Associate in Medicine, Harvard Medical School. Philadelphia and London, 1950, W. B. Saunders Company, 187 pages and 110 figures. Price $4.50.

This is an excellent small text on electrocardiography. It is divided into two parts.

The first deals with the basic principles of electrocardiography and sets forth these principles in a clear and fundamental fashion. Instead of expounding this subject from the empirical point of view, the author has, with clarity, explained why certain patterns should be as they are, why certain changes in the excitation wave should give certain patterns, and why variations in muscle mass or muscle injury should alter the electrocardiogram. With these fundamental concepts in mind, the student of electrocardiography can account for innumerable variations in degree from the normal.

In the second part, the author makes clinical application of these principles to explain the normal electrocardiogram and how it is influenced by various pathological states. This is kept on a scientific plane by referring the reader to the pertinent basic knowledge discussed in Part I. Without these correlations, Part II would be merely a revision of the earlier clinical application of electrocardiography to abnormalities in the conducting and myocardial systems.

It will be noted that there is no mention of the auricle. This is as it should be in a text of this character as it deals entirely with the fundamental concepts of electrocardiography and with clinical conditions to serve as texts for degrees of deviation from the so-called normal. It will be further noted that the author has cited no references. This also is as it should be as he does not enter into controversy but lays down basic principles to be applied.

This text is to be highly recommended to any who seriously wish to study and comprehend this subject.

J. C. M.